3-8-00

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PATENT

Docket No. 1849.16102-A CIP 2

Box Patent Application

Commissioner of Patents and Trademarks

Washington, D.C. 20231

NEW APPLICATION TRANSMITTAL

Transmitted herewith for filing is the patent application of

Inventor(s): ***Olexander Hnojewyj; Charles Milo; Gregory Cruise***

WARNING: Patent must be applied for in the name(s) of all of the actual inventor(s). 37 CFR 1.41(a) and 1.53(b).

For (title): ***Biocompatible Material Composition Adaptable to Diverse Therapeutic Indications***

1. Type of Application

This new application is for a(n) *(check one applicable item below):*

[ ] Original

[ ] Design

[ ] Plant

WARNING: Do not use this transmittal for a completion in the U.S. of an International Application under 35 U.S.C. 371(c)(4) unless the International Application is being filed as a divisional, continuation or continuation-in-part application.

NOTE: If one of the following 3 items apply then complete and attach ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF A PRIOR U.S. APPLICATION CLAIMED and a NOTIFICATION IN PARENT APPLICATION OF THE FILING OF THIS CONTINUATION APPLICATION.

[ ] Divisional

[ ] Continuation

[x] Continuation-in-part (CIP)

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this New Application Transmittal and the documents referred to as enclosed therein are being deposited with the United States Postal Service on this date March 7, 2000 in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EL504288586US addressed to the: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Judith Biebel

(type or print name of person mailing paper)

Judith A Biebel

(Signature of person mailing paper)

NOTE: Each paper or fee referred to as enclosed herein has the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 Cfr 1.10(b).

2. **Benefit of Prior U.S. Application(s) (35 USC 120)**

NOTE: If the new application being transmitted is a divisional, continuation or a continuation-in-part of a parent case, or where the parent case is an International Application which designated the U.S., then check the following item and complete and attach ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED.

[x] The new application being transmitted claims the benefit of prior U.S. application(s) and enclosed are ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED.

3. **Papers Enclosed Which Are Required For Filing Date Under 37 CFR 1.53(b) (Regular) or 37 CFR 1.153 (Design) Application**

38 Pages of specification

18 Pages of claims

01 Pages of Abstract

05 Sheets of drawing

[ ] formal

[x] informal

WARNING: DO NOT submit original drawings. A high quality copy of the drawings should be supplied when filing a patent application. The drawings that are submitted to the Office must be on strong, white, smooth, and non-shiny paper and meet the standards according to § 1.84. If corrections to the drawings are necessary, they should be made to the original drawing and a high-quality copy of the corrected original drawing then submitted to the Office. Only one copy is required or desired. Comments on proposed new 37 CFR 1.84. Notice of March 9, 1988 (1990 o.G. 57-62).

NOTE: Identifying indicia such as the serial number, group and unit, title of the invention, attorney's docket number, inventor's name, number of sheets, etc., not to exceed 23/4 inches (7.0 cm.) in width may be placed in a centered location between the side edges within three fourths inch (19.1 mm.) of the top edge. Either this marking technique on the front of the drawing or the placement, although not preferred, of this information and the title of the invention on the back of the drawings is acceptable." Proposed 37 CFR 1.84(1). Notice of March 9, 1988 (1090 O.G. 57-62).

4. **Additional papers enclosed**

[ ] Preliminary Amendment

[ ] Information Disclosure Statement (37 CFR 1.98)

[ ] Form PTO-1449

[ ] Citations

[ ] Declaration of Biological Deposit

[ ] Submission of "Sequence Listing," computer readable copy and/or amendment pertaining thereto for biotechnology invention containing nucleotide and/or amino acid sequence.

[ ] Authorization of Attorney(s) to Accept and Follow Instructions from Representative

[ ] Special Comments

[ ] Other

5. **Declaration or oath**

[ ] Enclosed

executed by *(check all applicable boxes)*

[ ] inventor(s).

[ ] legal representative of inventor(s). 37 CFR 1.42 or 1.43

[ ] joint inventor or person showing a proprietary interest on behalf of inventor who refused to sign or cannot be reached.

[ ] this is the petition required by 37 CFR 1.47 and the statement required by 37 CFR 1.47 is also attached. *See item 13 below for fee.*

[x] Not Enclosed.

WARNING: *Where the filing is a completion in the U.S. of an International Application but where a declaration is not available or where the completion of the U.S. application contains subject matter in addition to the International Application the application may be treated as a continuation or continuation-inpart, as the case may be, utilizing ADDED PAGE FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION CLAIMED.*

[x] Application is made by a person authorized under 37 CFR 1.41(c) on behalf of all the above named inventor(s). (The declaration or oath, along with the surcharge required by 37 CFR 1.16(E) can be filed subsequently).

NOTE: *It is important that all the correct inventor(s) are named for filing under 37 CFR 1.41(c) and 1.53(b).*

[ ] Showing that the filing is authorized. *(Not required unless called into question. 37 CFR 1.41(d).*

6. **Inventorship Statement**

WARNING: *If the named inventors are each not the inventors of all the claims an explanation, including the ownership of the various claims at the time the last claimed invention was made, should be submitted.*

The inventorship for all the claims in this application are:

[x] The same

or

[ ] Are not the same. An explanation, including the ownership of the various claims at the time the last claimed invention was made,

[ ] is submitted.

[ ] will be submitted.

7. **Language**

NOTE: *An application including a signed oath or declaration may be filed in a language other than English. A verified English translation of the non-English language application and the processing fee of $130.00 required by 37 CFR 1.17(k) is required to be filed with the application or within such time as may be set by the Office. 37 CFR 1.52(d).*

NOTE: *A non-English oath or declaration in the form provided or approved by the PTO need not be translated. 37 CFR 1.69(b).*

[x] English

[ ] non-English

[ ] the attached translation is a verified translation. 37 CFR 1.52(d).

8. Assignment

[x] An assignment of the invention to Advanced Closure Systems

[ ] is attached. A separate [ ] "COVER SHEET FOR ASSIGNMENT (DOCUMENT) ACCOMPANYING NEW PATENT APPLICATION" or [ ] FORM PTO 1595 is also attached.

[x] will follow.

NOTE: "If an assignment is submitted with a new application, send two separate letters-one for the application and one for the assignment." Notice of May 4, 1990 (1114 O.G. 77-78).

WARNING: A newly executed "CERTIFICATE UNDER 37 CFR 3.73(b)" must be filed when a continuation--in-part application is filed by an assignee. Notice of April 30, 1993, 1150 O.G. 62-64.

9. Certified Copy

Certified copy(ies) of application(s)

(country)	(appln. no.)	(filed)
(country)	(appln. no.)	(filed)
(country)	(appln. no.)	(filed)

from which priority is claimed

[ ] is(are) attached.

[ ] will follow.

NOTE: The foreign application forming the basis for the claim for priority must be referred to in the oath or declaration. 37 CFR 1.55(A) AND 1.63.

NOTE: This item is for any foreign priority for which the application being filed directly relates. If any parent U.S. application or International Application from which this application claims benefit under 35 U.S.C. 120 is itself entitled to priority from a prior foreign application then complete item 18 on the ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED.

10. Fee Calculation (37 CFR 1.16)

A. [x] Regular application

CLAIMS AS FILED

	Number filed		Number Extra		Rate	Basic Fee 37 CFR 1.16(a) $690.00
Total Claims (37 CFR 1.16(c))	454	-20 =	434	X	$ 18.00	7812.00
Independent Claims (37 CFR 1.16(b))	16	-3 =	13	X	$78.00	1014.00
Multiple dependent claim(s), if any (37 CFR 1.16(d))				+	$260.00	260.00

[ ] Amendment cancelling extra claims enclosed.

[ ] Amendment deleting multiple-dependencies enclosed.

[ ] Fee for extra claims is not being paid at this time.

NOTE: If the fees for extra claims are not paid on filing they must be paid or the claims cancelled by amendment, prior to the expiration of the time period set for response by the Patent and Trademark Office in any notice of fee deficiency. 37 CFR 1.16(d).

Filing Fee Calculation $ 9776.00

B. [ ] Design application
($330.00-37 CFR 1.16(f))

Filing Fee Calculation $ _____

C. [ ] Plant application
($540.00-37 CFR 1.16(g))

Filing fee calculation $ _____

11. **Small Entity Statement(s)**

[x] Verified Statement(s) that this is a filing by a small entity under 37 CFR 1.9 and 1.27 will follow.

Filing Fee Calculation (50% of A, B or C above) $ 4888.00

NOTE: Any excess of the full fee paid will be refunded if a verified statement and a refund request are filed within 2 months of the date of timely payment of a full fee. 37 CFR 1.28(a).

12. **Request for International-Type Search (37 CFR 1.104(d)) (complete, if applicable)**

[ ] Please prepare an international-type search report for this application at the time when national examination on the merits takes place.

13. **Fee Payment Being Made At This Time**

[x] Not Enclosed

[x] No filing fee is to be paid at this time. *(This and the surcharge required by 37 CFR 1.16(e) can be paid subsequently.)*

[ ] Enclosed

[ ] basic filing fee $ _____

[ ] recording assignment
($40.00; 37 CFR 1.21(h))(See attached "COVER SHEET FOR ASSIGNMENT ACCOMPANYING NEW APPLICATION".) $ _____

[ ] petition fee for filing by other than all the inventors or person on behalf of the inventor where inventor refused to sign or cannot be reached. ($130.00; 37 CFR 1.47 and 1.17(h)) $ _____

[ ] for processing an application with a specification in a non-English language. ($130.00; 37 CFR 1.52(d) and 1.17(k) $ _____

[ ] processing and retention fee
($130.00; 37 CFR 1.53(d) and 1.21(l))

[ ] fee for international-type search report ($40.00; 37 CFR 1.21(e)). $ _____

NOTE: 37 CFR 1.21(l) establishes a fee for processing and retaining any application which is abandoned for failing to complete the application pursuant to 37 CFR 1.53(d) and this, as well as the changes to 37 CFR 1.53 and 1.78, indicate that in order to obtain the benefit of a prior U.S. application, either the basic filing fee must be paid or the processing and retention fee of § 1.21(l) must be paid within 1 year from notification under § 53(d).

Total fees enclosed $ - 0 -

14. Method of Payment of Fees

[ ] Check in the amount of $____.

[ ] Charge Account No. __ in the amount of $ ___. A duplicate of this transmittal is attached.

NOTE: Fees should be itemized in such a manner that it is clear for which purpose the fees are paid. 37 CFR 1.22(b).

15. Authorization to Charge Additional Fees

WARNING: If no fees are to be paid on filing the following items should not be completed.

WARNING: Accurately count claims, especially multiple dependent claims, to avoid unexpected high charges, if extra claim charges are authorized.

[ ] The Commissioner is hereby authorized to charge the following additional fees by this paper and during the entire pendency of this application to Account No. _____

[ ] 37 CFR 1.16(a), (f) or (g) (filing fees)

[ ] 37 CFR 1.16(b), (c) and (d) (presentation of extra claims)

NOTE: Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 CFR 1.16(d)), it might be best not to authorize the PTO to charge additional claim fees, except possibly when dealing with amendments after final action.

[ ] 37 CFR 1.16(e) (surcharge for filing the basic filing fee and/or declaration on a date later than the filing date of the application)

[ ] 37 CFR 1.17 (application processing fees)

WARNING: While 37 CFR 1.17(A), (b), (c) and (d) deal with extensions of time under § 1.136(A) this authorization should be made only with the knowledge that: "submission of the appropriate extension fee under 37 C.F.R. 1.136(A) is to no avail unless a request or petition for extension is filed." (Emphasis added). Notice of November 5, 1985 (1060 O.G.27).

[ ] 37 CFR 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 CFR 1.311(b))

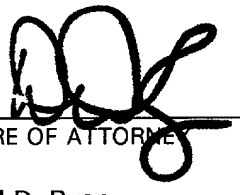
NOTE: Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 CFR 1.311(b).

NOTE: 37 CFR 1.28(b) requires "Notification of any change in loss of entitlement to small entity status must be filed in the application ... prior to paying, or at the time of paying, ... issue fee". From the wording of 37 CFR 1.28(b): (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.

16. Instructions As To Overpayment

[ ] credit Account No. _____

[ ] refund



SIGNATURE OF ATTORNEY

Reg. No. 29,243

Daniel D. Ryan
(type or print name of attorney)

Tel. No. (414) 271-6555

RYAN KROMHOLZ & MANION, S.C.
633 West Wisconsin Avenue
(P.O. Address)
Milwaukee, Wisconsin 53203

[x] **Incorporation by reference of added pages**

Check the following item if the application in this transmittal claims the benefit of prior U.S. application(s) (including an international application entering the U.S. stage as a continuation, divisional or C-I-P application) and complete and attach the ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED

[x] Plus Added Pages For New Application Transmittal Where Benefit Of Prior U.S. Application(s) Claimed

Number of pages added 4

[ ] Plus Added Pages For Papers Referred To In Item 4 Above

Number of pages added _____

[ ] Plus "Assignment Cover Letter Accompanying New Application"

Number of pages added _____

[ ] **Statement Where No Further Pages Added**

(If no further pages form a part of this Transmittal then end this Transmittal with this page and check the following item)

[ ] This transmittal ends with this page.

PATENT

ADDED PAGES FOR APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED

NOTE: "In order for an application to claim the benefit of a prior filed copending national application, the prior application must name as an inventor at least one inventor named in the later filed application and disclose the named inventor's invention claimed in at least one claim of the later filed application in the manner provided by the first paragraph of 35 U.S.C. 112." 37 CFR 1.78(a).

NOTE: "IN ADDITION THE PRIOR APPLICATION MUST BE (1) COMPLETE AS SET FORTH IN S 1.51, OR (2) ENTITLED TO A FILING DATE AS SET FORTH IN S 1.53(B) AND INCLUDE THE BASIC FILING FEE SET FORTH IN S 1.16; OR (3) ENTITLED TO A FILING DATE AS SET FORTH IN S 1.53(B) AND HAVE PAID THEREIN THE PROCESSING AND RETENTION FEE SET FORTH IN S 1.21(L) WITHIN THE TIME PERIOD SET FORTH IN S 1.53(D)."37 CFR 1.78(A).

17. Relate Back-35 U.S.C. 120

NOTE: "ANY APPLICATION CLAIMING THE BENEFIT OF A PRIOR FILED COPENDING NATIONAL OR INTERNATIONAL APPLICATION MUST CONTAIN OR BE AMENDED TO CONTAIN IN THE FIRST SENTENCE OF THE SPECIFICATION FOLLOWING THE TITLE A REFERENCE TO SUCH PRIOR APPLICATION IDENTIFYING IT BY SERIAL NUMBER AND FILING DATE OR INTERNATIONAL APPLICATION NUMBER AND INTERNATIONAL FILING DATE AND INDICATING THE RELATIONSHIP OF THE APPLICATIONS." 37 CFR 1.78(A). SEE ALSO THE NOTICE OF APRIL 28, 1987 (1079 O.G. 32 TO 46).

[x] The specification contains the following information:

Related Application:

This application is a continuation-in-part of United States Patent Application Serial No. 09/283,535, filed April 1, 1999, and entitled "Compositions, Systems, and Methods for Arresting or Controlling Bleeding or Fluid Leakage in Body Tissue," which is itself a continuation-in-part of United States Patent Application Serial No. 09/188,083, filed November 6, 1998 and entitled Compositions, Systems, and Methods for Creating In Situ, Chemically Cross-Linked, Mechanical Barriers."

NOTE: THE PROPER REFERENCE TO A PRIOR FILED PCT APPLICATION WHICH ENTERED THE U.S. NATIONAL PHASE IS THE U.S. SERIAL NUMBER AND THE FILING DATE OF THE PCT APPLICATION WHICH DESIGNATED THE U.S.

NOTE: (1) WHERE THE APPLICATION BEING TRANSMITTED ADDS SUBJECT MATTER TO THE INTERNATIONAL APPLICATION THEN THE FILING CAN BE AS A CONTINUATION-IN-PART OR (2) IT IS DESIRED TO DO SO FOR OTHER REASONS, E.G. WHERE NO DECLARATION IS AVAILABLE, NO ENGLISH TRANSLATION IS AVAILABLE OR NO FEE IS TO BE PAID ON FILING THEN THE FILING CAN BE AS A CONTINUATION. IN THESE CASES THE INTERNATIONAL APPLICATION DESIGNATING THE U.S. IS TREATED AS THE PARENT CASE IN THE U.S. AND IS AN ALTERNATIVE TO THE COMPLETION OF THE INTERNATIONAL APPLICATION UNDER 35 U.S.C. 371(C)(4) WHICH MUST MEET THE REQUIREMENTS OF 37 CFR 1.61(A). THIS ALTERNATIVE PERMITS THE COMPLETION OF THE FILING REQUIREMENTS WITHIN ANY TERM SET BY THE PTO UNDER 37 CFR 1.53(D) TO WHICH THE EXTENSION PROVISIONS OF 37 CFR 1.136(A) APPLY. (WHEREAS, IF THE FILING IS AS AN INTERNATIONAL APPLICATION ENTERING THE U.S. STAGE THEN THE FEE, DECLARATION AND/OR ENGLISH TRANSLATION (WHERE NECESSARY) IS DUE WITHIN 20 MONTHS OF THE PRIORITY DATE BUT CAN BE PAID WITHIN 22 MONTHS OF THE PRIORITY DATE (OR IS DUE WITHIN 30 MONTHS OF THE PRIORITY DATE BUT CAN BE SUBMITTED WITHIN 32 MONTHS OF THE PRIORITY DATE) WITH THE SURCHARGES SET FORTH IN 37 CFR 1.492(E), (F) AND 37 CFR 1.495(C); HOWEVER, THE PROVISIONS OF 37 CFR 1.136 DO NOT APPLY TO THIS 22 OR (32 MONTH) PERIOD. 37 CFR 1.61(B).)

NOTE: THE DEADLINE FOR ENTERING THE NATIONAL PHASE IN THE U.S. FOR AN INTERNATIONAL APPLICATION WAS CLARIFIED IN THE NOTICE OF APRIL 28, 1987 (1079 O.G. 32 TO 46) AS FOLLOWS:

"The Patent and Trademark Office considers the International application to be pending until the 22nd month from the priority date if the United States has been designated and no Demand for International Preliminary Examination has been filed prior to the expiration of the 19th month from the priority date and until the 32nd month from the priority date if a Demand for International Preliminary Examination which elected the United States of America has been filed prior to the expiration of the 19th month from the priority date, provided that a copy of the international application has been communicated to the Patent and Trademark Office within the 20 or 30 month period respectively. If a copy of the international application has not been communicated to the Patent and Trademark Office within the 20 or 30 month period respectively, the international application becomes abandoned as to the United States 20 or 30 months from the priority date respectivley. These periods have been placed in the rules as paragraph (h) of S 1.494 and paragraph (i) of S 1.495. A continuing application under 35 U.S.C. 365(c) and 120 may be filed anytime during the pendency of the international application."

18. Relate Back-35 U.S.C. 119 Priority Claim for Prior Application

The prior U.S. application(s), including any prior International Application designating the U.S., identified above in item 17, in turn itself claim(s) foreign priority (ies) as follows:

country	appl. no.	filed on

The certified copy (ies) has (have)

[ ] been filed on _____ in prior application 0 /_____ which was filed on _____.

[ ] is (are) attached

WARNING: THE CERTIFIED COPY OF THE PRIORITY APPLICATION WHICH MAY HAVE BEEN COMMUNICATED TO THE PTO BY THE INTERNATIONAL BUREAU MAY NOT BE RELIED ON WITHOUT ANY NEED TO FILE A CERTIFIED COPY OF THE PRIORITY APPLICATION IN THE CONTINUING APPLICATION. THIS IS SO BECAUSE THE CERTIFIED COPY OF THE PRIORITY APPLICATION COMMUNICATED BY THE INTERNATIONAL BUREAU IS PLACED IN A FOLDER AND IS NOT ASSIGNED A U.S. SERIAL NUMBER UNLESS THE NATIONAL STAGE IS ENTERED. SUCH FOLDERS ARE DISPOSED OF IF THE NATIONAL STAGE IS NOT ENTERED. THEREFORE SUCH CERTIFIED COPIES MAY NOT BE AVAILABLE IF NEEDED LATER IN THE PROSECUTION OF A CONTINUING APPLICATION. AN ALTERNATIVE WOULD BE TO PHYSICALLY REMOVE THE PRIORITY DOCUMENTS FROM THE FOLDERS AND TRANSFER THEM TO THE CONTINUING APPLICATION. THE RESOURCES REQUIRED TO REQUEST TRANSFER, RETRIEVE THE FOLDERS, MAKE SUITABLE RECORD NOTATIONS, TRANSFER THE CERTIFIED COPIES, ENTER AND MAKE A RECORD OF SUCH COPIES IN THE CONTINUING APPLICATION ARE SUBSTANTIAL. ACCORDINGLY, THE PRIORITY DOCUMENTS IN FOLDERS OF INTERNATIONAL APPLICATIONS WHICH HAVE NOT ENTERED THE NATIONAL STAGE MAY NOT BE RELIED ON. NOTICE OF APRIL 28, 1987 (1079 O.G. 32 TO 46).

19. Maintenance of Copendency of Prior Application

NOTE: THE PTO FINDS IT USEFUL IF A COPY OF THE PETITION FILED IN THE PRIOR APPLICATION EXTENDING THE TERM FOR RESPONSE IS FILED WITH THE PAPERS CONSTITUTING THE FILING OF THE CONTINUATION APPLICATION. NOTICE OF NOVEMBER 5, 1985 (1060 O.G. 27).

A. [ ] Extension of time in prior application

(This item MUST BE COMPLETED AND THE PAPERS FILED IN THE PRIOR APPLICATION IF THE PERIOD SET IN THE PRIOR APPLICATION HAS RUN)

[ ] A petition, fee and response extends the term in the pending prior application until _____.

[ ] A copy of the petition filed in prior application is attached

B. [ ] Conditional Petition for Extension of Time in Prior Application

(complete this item if previous item not applicable)

[ ] A conditional petition for extension of time is being filed in the pending prior application.

[ ] A copy of the conditional petition filed in the prior application is attached

20. Further Inventorship Statement Where Benefit of Prior Application(s) Claimed

NOTE: IF THE CONTINUATION, CONTINUATION-IN-PART, OR DIVISIONAL APPLICATION IS FILED BY LESS THAN ALL THE INVENTORS NAMED IN THE PRIOR APPLICATION A STATEMENT MUST ACCOMPANY THE APPLICATION WHEN FILED REQUESTING DELETION OF THE NAMES OF THE PERSON OR PERSONS WHO ARE NOT INVENTORS OF THE INVENTION BEING CLAIMED IN THE CONTINUATION, CONTINUATION-IN-PART, OR DIVISIONAL APPLICATION. 37 CFR 1.62(A) [EMPHASIS ADDED]. (DEALING WITH THE FILE WRAPPER CONTINUATION SITUATION).

NOTE: IN THE CASE OF A CONTINUATION-IN-PART APPLICATION WHICH ADDS AND CLAIMS ADDITIONAL DISCLOSURE BY AMENDMENT, AN OATH OR DECLARATION AS REQUIRED BY S 1.63 MUST BE FILED. IN THOSE SITUATIONS WHERE A NEW OATH OR DECLARATION IS REQUIRED DUE TO ADDITIONAL SUBJECT MATTER BEING CLAIMED, ADDITIONAL INVENTORS MAY BE NAMED IN THE CONTINUING APPLICATION. IN A CONTINUATION OR DIVISIONAL APPLICATION WHICH DISCLOSES AND CLAIMS ONLY SUBJECT MATTER DISCLOSED IN A PRIOR APPLICATION, NO ADDITIONAL OATH OR DECLARATION IS REQUIRED AND THE APPLICATION MUST NAME AS INVENTORS THE SAME OR LESS THAN ALL THE INVENTORS IN THE PRIOR APPLICATION. 37 CFR 1.60(C). (DEALING WITH THE CONTINUATION SITUATION).

(complete applicable item (a), (b) and/or (c) below)

(a) [ ] This application discloses and claims only subject matter disclosed in the prior application whose particulars are set out above and the inventor(s) in this application are

[ ] the same.
[ ] less than those named in the prior application and it is requested that the following inventor(s) identified for the prior application be deleted:

_____
(type name(s) of inventor(s) to be deleted)

(b) [x] This application discloses and claims additional disclosure and a new declaration or oath is being filed. With respect to the prior application the inventor(s) in this application are

[ ] the same.
[x] the following additional inventor(s) have been added

Charles Milo
(type name(s) of inventor(s) to be added)

(c) The inventorship for all the claims in this application are

[x] the same.
[ ] not the same, and an explanation, including the ownership of the various claims at the time the last claimed invention was made

[ ] is submitted.
[ ] will be submitted.

21. Abandonment of Prior Application (if applicable)

[ ] Please abandon the prior application at a time while the prior application is pending or when the petition for extension of time or to revive in that application is granted and when this application is granted a filing date so as to make this application copending with said prior application.

NOTE: ACCORDING TO THE NOTICE OF MAY 13, 1983 (103, TMOG 6-7) THE FILING OF A CONTINUATION OR CONTINUATION-IN-PART APPLICATION IS A PROPER RESPONSE WITH RESPECT TO A PETITION FOR EXTENSION OF TIME OR A PETITION TO REVIVE AND SHOULD INCLUDE THE EXPRESS ABANDONMENT OF THE PRIOR APPLICATION CONDITIONED UPON THE GRANTING OF THE PETITION AND THE GRANTING OF A FILING DATE TO THE CONTINUING APPLICATION.

22. Petition for Suspension of Prosecution for the Time Necessary to File an Amendment

WARNING: THE CLAIMS OF A NEW APPLICATION MAY BE FINALLY REJECTED IN THE FIRST OFFICE ACTION IN THOSE SITUATIONS WHERE (1) THE NEW APPLICATION IS A CONTINUING APPLICATION OF, OR A SUBSTITUTE FOR, AN EARLIER APPLICATION, AND (2) ALL THE CLAIMS OF THE NEW APPLICATION (A) ARE DRAWN TO THE SAME INVENTION CLAIMED IN THE EARLIER APPLICATION, AND (B) WOULD HAVE BEEN PROPERLY FINALLY REJECTED ON THE GROUNDS OF ART OF RECORD IN THE NEXT OFFICE ACTION IF THEY HAD BEEN ENTERED IN THE EARLIER APPLICATION." MPEP, S 706.07(B).

NOTE: WHERE IT IS POSSIBLE THAT THE CLAIMS ON FILE WILL GIVE RISE TO A FIRST ACTION FINAL FOR THIS CONTINUATION APPLICATION AND FOR SOME REASON AN AMENDMENT CANNOT BE FILED PROMPTLY (E.G., EXPERIMENTAL DATA IS BEING GATHERED) IT MAY BE DESIRABLE TO FILE A PETITION FOR SUSPENSION OF PROSECUTION FOR THE TIME NECESSARY.

(check the next item, if applicable)

[ ] There is provided herewith a Petition To Suspend Prosecution for the Time Necessary to File An Amendment (New Application Filed Concurrently)

Patent

Docket No. 1849.16102-A CIP 2

BIOCOMPATIBLE MATERIAL COMPOSITION ADAPTABLE TO DIVERSE THERAPEUTIC INDICATIONS

RELATED APPLICATION

This application is a continuation-in-part of United States Patent Application Serial No. 09/283,535, filed April 1, 1999, and entitled "Compositions, Systems, and Methods for Arresting or Controlling Bleeding or Fluid Leakage in Body Tissue," which is itself a continuation-in-part of United States Patent Application Serial No. 09/188,083, filed November 6, 1998 and entitled "Compositions, Systems, and Methods for Creating In Situ, Chemically Cross-Linked, Mechanical Barriers."

FIELD OF THE INVENTION

The invention generally relates to the composition of biocompatible materials and their application to body tissue to affect desired therapeutic results.

BACKGROUND OF THE INVENTION

There are many therapeutic indications today that pose problems in terms of technique, cost efficiency, or efficacy, or combinations thereof.

For example, following an interventional procedure, such as angioplasty or stent placement, a 5 Fr to 8 Fr arteriotomy remains. Typically, the bleeding from the arteriotomy is controlled through pressure applied by hand, by sandbag, or by C-clamp for at least 30 minutes. While pressure will ultimately achieve hemostasis, the excessive use and cost of health care personnel is incongruent with managed care goals.

As another example, blood leaks from a variety

of different tissues are common during surgical procedures. Examples include following trauma to or resection of the liver, spleen, or kidney, vascular anastomoses, and bone bleeding during sternotomy. Presently, the surgeon has a limited number of options to control bleeding, typically pressure, thrombin, fibrin glue, bone wax, and/or collagen sponge.

Likewise, controlling air leaks from lung tissue is difficult to achieve during thoracic procedures. Examples include lung resections and lung volume reduction surgery. Presently, the surgeon has a limited number of options to control air leaks, typically a chest tube is required to remove air from the thoracic cavity. The presence of a chest tube extends the stay of the patient in the hospital. If the air leaks could be sealed at the time of surgery, the patient would be able to be discharged sooner.

Similarly, controlling liquid leaks from tissue is difficult to achieve during surgical procedures. Examples include dural leaks and lymph fluid leaks during surgical procedures. Typically, the surgeon does not control dural leaks due to the lack of an effective dural substitute, potentially increasing the risk of transmission of infectious agents. Controlling solid leaks from tissue is likewise difficult to achieve during surgical procedures. Examples include bowel leaks during surgical procedures. Typically, the surgeon controls bowel leaks by adding additional sutures until the leak is no longer observed.

As another example, adhesions are abnormal, fibrous connections of tissues that are not normally connected. Adhesions are formed as a part of the normal wound healing response of tissue, however they can result in infertility and pain. Several products are available for use by the surgeon to prevent the formation of

adhesions, however the efficacy of the marketed products has not been conclusively demonstrated.

Likewise, tissue voids can be created by a variety of procedures. For example, the ABBI™ system, marketed by United States Surgical Company, is a minimally invasive breast biopsy system that cores out breast tissue for analysis by a pathologist. The cores range in size from five to twenty millimeters in diameter. Following the removal of the core, a tissue void is created and the surrounding tissue oozes blood into the void.

Various tissues can also be augmented to create a more desired appearance. For example, an injectable bovine collagen, marketed by Inamed Corporation, can be used to reduce the appearance of facial wrinkles or create the appearance of fuller lips. While the treatment is effective, the persistence is brief.

The treatment of arterio-venous malformations (AVM's) and aneurysms provide further examples. AVM's are tangled masses of blood vessels that are neither arteries nor veins, commonly found in the brain, possibly leading to hemorrhagic stroke. Clinically, AVM's are treated by surgical removal. Before removal, the AVM must be embolized to prevent uncontrolled bleeding. Aneurysms are abnormal widening of portions of blood vessels, leading to an increased chance of rupture. Clinically, aneurysms are treated by surgical removal, stent-grafting, or coils. Another possible treatment modality is to fill the ballooned section of the blood vessel with a biomaterial, protecting and strengthening the diseased tissue.

There is also an increasing trend towards site-specific delivery of pharmaceuticals and vectors. The main advantage is high dose delivery at the diseased tissue, but a low systemic dose. For example, a depot

filled with anti-cancer agents can be placed directly on a tumor. The areas surrounding the depot have a high concentration of the anti-cancer agent, but the systemic dose is low, minimizing side effects.

Cells, as well as pharmaceuticals and vectors, can be likewise delivered to a diseased tissue site. The cells could be genetically modified, autologous, or derived from other sources.

There remains a demand for biomaterials that improve the technique, cost efficiency, and efficacy of these and other therapeutic indications.

SUMMARY OF THE INVENTION

One aspect of the invention provides a biocompatible genus material composition upon which a diverse family of biocompatible material composition species can be created. The species are remarkably well adapted to specific therapeutic indications, although the therapeutic indications themselves differ significantly.

In one embodiment, the genus biocompatible material comprises a mixture of a protein solution and a polymer solution. The polymer solution includes a derivative of a hydrophilic polymer with a functionality of at least three. Upon mixing, the protein solution and the polymer solution cross-link to form a non-liquid, three-dimensional network.

In one embodiment, the network degrades over time back to a liquid form. In this embodiment, the polymer includes a degradation control region selected to achieve a desired degradation period. The degradation control region can selected to form different species, each having a different degradation period. The degradation periods can vary, e.g., within a range of between about 1 day to greater than 500 days.

In one embodiment, the polymer includes a cross-linking group selected to achieve a desired cross-

linking period. The cross-linking group can be selected to achieve different species, each having its own desired cross-linking period. The cross-linking periods can vary, e.g., within a range of from less than one second to greater than 10 hours.

In one embodiment, the polymer includes both a degradation control region and a cross-linking group. In this embodiment, each region can be individually selected to form different species, each species having its own period of degradation and cross-linking customized to achieve one or therapeutic objectives.

Another aspect of the invention provides systems making use of the diverse species for different therapeutic indications. Each system includes instructions for forming a mixture of the protein solution and polymer solution and for applying the mixture to accomplish a particular therapeutic objective. The particular therapeutic objective can be, e.g., sealing a vascular puncture site, sealing tissue from blood or gas or liquid leaks, sealing tissue from solid leaks, preventing post operative adhesions, repairing a tissue void, augmenting tissue, embolizing an arterio-venous malformation, filling an aneurysm, delivering a pharmaceutical, or delivering cells.

Another aspect of the invention provides a biocompatible material comprising a mixture of a protein solution and a polymer solution which, upon mixing, cross-link to form a non-liquid, three-dimensional network. The material includes an agent that undergoes color change in response to cross-linking of the mixture.

In one embodiment, the agent undergoes color change in response to change in pH during cross-linking.

In one embodiment, the agent exhibits a first color when the mixture is in a liquid state and a second color, different than the first color, when the mixture

forms the non-liquid, three-dimensional network.

In one embodiment, the agent exhibits a first color when the mixture is in transition between a liquid state and the non-liquid, three dimensional network, and a second color, different than the first color, when the mixture forms the non-liquid, three-dimensional network.

Features and advantages of the inventions are set forth in the following Description and Drawings, as well as in the appended Claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a diagrammatic view of a genus composition of a biocompatible material that forms the basis for multiple composition species, each well adapted to a specific therapeutic indication;

Fig. 2 is a diagrammatic view of a system comprising first and second functional kits useful for applying or delivering a given composition species shown in Fig. 1 at the intended delivery site;

Fig. 3 is a plane view of the details of representative kits shown in Fig. 2, one kit containing the basic formative components of the genus composition, and the other kit containing a mixing/dispensing assembly for the species;

Fig. 4 is a perspective view of a representative mixing/dispensing assembly contained in the second kit shown in Fig. 3;

Fig. 5 is a flowchart illustrating a methodology for developing species compositions based upon the composition genus shown in Fig. 1; and

Fig. 6 is a graph showing the changes on pH as a given species composition cross-links to form a solid three-dimensional network.

The invention may be embodied in several forms without departing from its spirit or essential characteristics. The scope of the invention is defined in

the appended claims, rather than in the specific description preceding them. All embodiments that fall within the meaning and range of equivalency of the claims are therefore intended to be embraced by the claims.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

I. Overview

Fig. 1 shows a genus composition 10 comprising a biocompatible material. The genus composition 10 is the basis for multiple material composition species 12.

The material composition species 12 of the genus composition 10 share several common fundamental characteristics, including:

(i) each composition species 12 is capable of being created *in situ* by mixing basic formative components, at least two of which are common throughout the genus;

(ii) the formative components, upon mixing, are capable of transforming from a liquid state to a biocompatible solid state (in a process called "gelation");

(iii) after gelation, the solid composition exhibits desired mechanical properties including adhesive strength, cohesive strength, and elasticity;

(iv) after gelation, the solid composition is also capable of transforming over time by physiological mechanisms from the solid state to a biocompatible liquid state, which can be cleared by the body (in a process called "degradation"); and

(v) each of the characteristics (ii) to (iv) can be selectively and independent controlled within wide physical ranges.

The common fundamental characteristics of the genus 10 give rise to a diverse family of biocompatible material composition species 12, having differing rates of gelation, rates of degradation, and mechanical

properties. The species are remarkably well adapted to specific therapeutic indications, although the therapeutic indications themselves differ significantly.

In the illustrated embodiment (see Fig. 1), the genus 10 is shown, by way of example, to contain twelve distinct species 12, each having a corresponding different therapeutic indication, as also listed in the following Table.

Table 1

Biocompatible Material Composition Species and Corresponding Therapeutic Indications

Species	Therapeutic Indication
1	Sealing Vascular Puncture Sites
2	Sealing Tissue From Blood Leaks
3	Sealing Tissue From Gas Leaks
4	Sealing Tissue From Liquid Leaks
5	Sealing Tissue From Solid Leaks
6	Preventing Post-Operative Adhesions
7	Repair of Tissue Voids
8	Augmentation of Tissue
9	Embolization of Arterio-Venous Malformations (AVM)
10	Filling of Aneurysms
11	Delivery of Pharmaceuticals
12	Delivery of Cells

As Fig. 2 shows, the common fundamental characteristics of the composition genus 10 make possible the development of a family of systems 14 for applying or delivering the species 12 at the intended treatment site. Each delivery system 14 shares certain common features, because of characteristics common to the genus

composition 10. Nevertheless, the delivery systems 14 also differ in specific respects, because each species 12 is tailored to meet the needs of a particular desired therapeutic indication.

Due to the common fundamental characteristics (i) and (ii) of the genus 10, each delivery system can be consolidated into two functional kits 16 and 18. The first kit 16 contains the basic formative components 20 of the genus composition 10. The kit 16 stores the basic formative components 20 in an unmixed condition prior to use. Certain aspects of the formative components 20 differ, according to the species 12 that the system 14 delivers or applies. Still, the fundamental characteristic of holding the basic formative components 20 in an unmixed condition until the instance of use is common to all delivery systems 14 of the family.

The second kit 18 contains a mixing/dispensing assembly 22 for each species 12. The mixing/dispensing assembly 22 brings the formative components 20 into intimate mixing contact in liquid form. The mixing/dispensing assembly 22 dispenses the liquid mixture to the intended therapeutic site, where the liquid mixture transforms *in situ* to a solid form. Among the delivery systems 14, certain aspects of the mixing/dispensing assembly 22 differ, according to requirements of the particular therapeutic indication. Still, the fundamental characteristic of the mixing of the formative components 20 for *in-situ* delivery is common to all delivery systems 14.

One or both kits 16 and 18 preferably includes instructions 24 for forming the liquid mixture and dispensing the liquid through the mixing/dispensing assembly 22 to achieve the particular desired therapeutic indication.84

II. The Genus Material Composition

In a preferred embodiment, the genus material composition 10 creates a non-liquid, three-dimensional network, termed a hydrogel. In this embodiment, there are two fundamental formative components common to the genus 10; namely, (i) a protein and (ii) a polymer.

The hydrogel is created by the reaction between one or more nucleophilic (electron donator)groups on one of the components (either the protein or the polymer) and one or more electrophilic (electrode withdrawing) groups on the other one of the components. The polymer can include one or more nucleophilic groups, such as amine groups (-NH2), or thiol groups (-SH), or one or more electrophilic groups, such as alcohol groups (-OH) or carboxyl groups (-COOH), or combinations thereof. Likewise, the sequence of amino acids forming the protein (which determines the protein's bioactivity) can provide nucleophilic reactivity (e.g., lysine, arginine, asparagine, glutamine, or cysteine), or can provide electrophilic reactivity (e.g., aspartic acid, glutamic acid, serine, threonine, or tyrosine), or both. The amino acid sequence of the protein can thus dictate the selection of the polymer, and vice versa.

The protein component most preferably takes the form of a protein solution with nucleophilic groups. The polymer component most preferably takes the form of a solution of an electrophilic derivative of a hydrophilic polymer with a functionality of at least three. In this arrangement, the electrophilic groups on the polymer react with the nucleophilic groups on the protein, to form the hydrogel.

Use of these two fundamental components permit the rates of gelation and degradation to be accurately and predictably controlled, to create a variety of different species 12. Furthermore, a genus material composition 10

based upon these two fundamental components possesses desirable mechanical properties, which can also be accurately and selective manipulated among the species. The ability to accurately and selectively control the rate of gelation, the rate of degradation, and the mechanical properties, allows the creation of diverse species, each optimized to meet the requirements of a particular therapeutic indication.

A. The Fundamental Protein Component

Suitable protein solutions for incorporation into the genus material 10 include non-immunogenic, hydrophilic proteins. Examples include serum, serum fractions, and solutions of albumin, gelatin, antibodies, fibrinogen, and serum proteins. In addition, water soluble derivatives of hydrophobic proteins can be used. Examples include solutions of collagen, elastin, chitosan, and hyaluronic acid. In addition, hybrid proteins with one or more substitutions, deletions, or additions in the primary structure may be used.

Furthermore, the primary protein structure need not be restricted to those found in nature. An amino acid sequence can be synthetically designed to achieve a particular structure and/or function and then incorporated into the genus material. The protein can be recombinantly produced or collected from naturally occurring sources.

The preferred protein solution is 25% human serum albumin, USP. Human serum albumin is preferred due to its biocompatibility and its ready availability.

B. The Fundamental Polymer Component

The fundamental polymer component of the genus material composition is a hydrophilic, biocompatible polymer that is electrophilically derivatized with a functionality of at least three. Examples include poly(ethylene glycol), poly(ethylene oxide), poly(vinyl

alcohol), poly(vinylpyrrolidinone), poly(ethyloxazoline), and poly(ethylene glycol)-co-poly(propylene glycol) block copolymers.

The fundamental polymer component is not restricted to synthetic polymers, as polysaccharides, carbohydrates, and proteins could be electrophilically derivatized with a functionality of at least three. In addition, hybrid proteins with one or more substitutions, deletions, or additions in the primary structure may be used as the polymer component. In this arrangement, the protein's primary structure is not restricted to those found in nature, as an amino acid sequence can be synthetically designed to achieve a particular structure and/or function and then incorporated into the material. The protein of the polymer component can be recombinantly produced or collected from naturally occurring sources.

Preferably, the polymer component is comprised of poly(ethylene glycol) (PEG) with a molecular weight between 1,000 and 30,000 g/mole, more preferably between 2,000 and 15,000, and most preferably between 10,000 and 15,000 g/mole. PEG has been demonstrated to be biocompatible and non-toxic in a variety of physiological applications. The preferred concentrations of the polymer are 5% to 35% w/w, more preferably 5% to 20% w/w. The polymer can be dissolved in a variety of aqueous solutions, but water is preferred.

The preferred polymer can be generally expressed as compounds of the formula:

$$PEG-(DCR-CG)_n$$

Where:

DCR is a degradation control region.

CG is a crosslinking group.

$n \geq 3$

While the preferred polymer is a multi-armed structure, a linear polymer with a functionality, or

reactive groups per molecule, of at least three can also be used. The utility of a given PEG polymer significantly increases when the functionality is increased to be greater than or equal to three. The observed incremental increase in functionality occurs when the functionality is increased from two to three, and again when the functionality is increased from three to four. Further incremental increases are minimal when the functionality exceeds about four.

The uses of PEG polymers with functionality of greater than three provides a surprising advantage. When crosslinked with higher functionality PEG polymers, the concentration of albumin can be reduced to 25% and below. Past uses of difunctional PEG polymers require concentrations of albumin well above 25%, e.g. 35% to 45%. Use of lower concentrations of albumin result in superior tissue sealing properties with increased elasticity, a further desired result. Additionally, 25% human serum albumin, USP is commercially available from several sources, however higher concentrations of human serum albumin, USP are not commercially available. By using commercially available materials, the dialysis and ultrafiltration of the albumin solution, as disclosed in the prior art, is eliminated, significantly reducing the cost and complexity of the preparation of the albumin solution.

C. The Resulting Genus 10 Hydrogel Composition

Upon mixing the fundamental protein solution component with the fundamental polymer solution, the non-liquid, three-dimensional network (i.e., the hydrogel) is formed.

To minimize the liberation of heat during the crosslinking reaction, the concentration of the crosslinking groups of the fundamental polymer component is preferably kept less than 5% of the total mass of the

reactive solution, and more preferably about 1% or less. The low concentration of the crosslinking group is also beneficial so that the amount of the leaving group is also minimized. In a typical clinical application, about 50 mg of a non-toxic leaving group is produced during the crosslinking reaction, a further desired result. In a preferred embodiment, the CG comprising an N-hydroxysuccinimide ester has demonstrated ability to participate in the crosslinking reaction with albumin without eliciting adverse immune responses in humans.

The genus material composition is well tolerated by the body, without invoking a severe foreign body response. Over a controlled period, the material is degraded by physiological mechanisms. Histological studies have shown a foreign body response consistent with a biodegradable material, such as VICRYL™ sutures. As the material is degraded, the tissue returns to a quiescent state. The molecules of the degraded genus hydrogel composition are cleared from the bloodstream by the kidneys and eliminated from the body in the urine. In a preferred embodiment of the invention, the material loses its physical strength during the first fifteen days, and totally resorbs in about four weeks.

III. Creating The Species Compositions

Species compositions are created from the genus composition by controlling the rate of gelation, or controlling the rate of degradation, or controlling the mechanical properties, or combinations thereof. The controlled properties of the species permit the use of the genus 10 material composition in diverse therapeutic indications.

A. Controlling the Rate of Gelation

The rate of gelation is optimally controlled by the selection of the crosslinking group (CG) and the reaction

pH. The concentration of the CG in the polymer solution, and the concentration of nucleophilic groups in the protein solution also can be used to control the rate of gelation, however changes in these concentrations typically result in changes in the mechanical properties of the hydrogel, as well as the rate of gelation.

The electrophilic CG is responsible for the crosslinking of the albumin, as well as binding the hydrogel to the surrounding tissue. The CG can be selected to selectively react with thiols, selectively react with amines, or react with thiols and amines. CG's that are selective to thiols include vinyl sulfone, N-ethyl maleimide, iodoacetamide, and orthopyridyl disulfide. CG's that are selective to amines include aldehydes. Non-selective electrophilic groups include active esters, epoxides, oxycarbonylimidazole, nitrophenyl carbonates, tresylate, mesylate, tosylate, and isocyanate. The preferred CG's are active esters, more preferred, an ester of N-hydroxysuccinimide. The active esters are preferred since they react rapidly with nucleophilic groups and have a non-toxic leaving group.

The rate of gelation can also be controlled by the selection of the reaction pH. At a lower pH, a larger fraction of nucleophilic groups is unavailable for reaction with the electrophile. At higher pH's, a larger fraction of nucleophilic groups is available for reaction with the electrophile. Ultimately, pH controls the concentration of nucleophilic groups that are available for reaction. The reaction pH is a useful mechanism to control the rate of gelation as it controls the rate without affecting the mechanical properties of the resulting hydrogel.

The reaction pH is optimally controlled by the buffer composition and concentration. Preferred buffer systems are sodium phosphate and sodium carbonate, which

can alone or in combination provide high or low pH buffers. A high pH buffer is preferred when high rates of gelation are desired. A low pH buffer is preferred for slower rates of gelation. The buffer concentration also plays a significant role in the rate of gelation. Because of the crosslinking, a leaving group is formed. In the preferred embodiment, the leaving group is acidic. So as the reaction proceeds, the pH drops and the rate of gelation slows. At higher buffer concentrations, the fast rate of gelation is sustained over the length of the reaction. At lower concentrations, the buffer system is saturated and no longer functions.

Through the selection of the CG and the reaction pH, the transformation of the material from a liquid to a solid can be controlled from less than 1 second to greater than 10 hours, more preferably less than 1 second to 10 minutes, and most preferably less than 1 second to 2 minutes.

It may be desirable to monitor the progression of the cross-linking. For example, when using Species 1 (to seal vascular puncture sites), it is desirable to know when the composition is semi-solid, which indicates that it is time to remove the catheter/introducer and apply pressure to the puncture site. It is also desirable to next know when the composition is solid, which indicates that pressure to the puncture site can be removed. The transitions from liquid to semi-solid and then from semi-solid to solid can be determined by timing the reaction.

The pH of the composition (protein and polymer) changes as cross-linking progresses (see Fig. 6). The change in pH during cross-linking for a given composition can be empirically determined using a spectophotometer. The pH is high (e.g., pH 9 to 10) when the polymer is liquid (time t_1 in Fig. 6). The pH is lower (e.g., pH 7) (time t_3 in Fig. 6) when the composition is solid. The pH

is at an intermediate value (e.g., pH 8) when the composition is in transition between liquid and solid (time t_2 in Fig. 6). The composition can include one or more colorimetric pH indicators to indicate, by color changes, the progression of the gelation.

For example, xylenol blue exhibits a purple color at pH 9-10, a yellow color at pH 8, and a yellow color at pH 7. Phenol red exhibits a red color at pH 9-10, a red color at pH 8, and a yellow color at pH 7. By including a mixture of xylenol blue and phenol red in the composition, the composition, as it cross-links, will exhibit a purple/blue color (mixture of purple and red) at time t_1 (pH greater than 9), indicating a liquid state; an orange color (mixture of yellow and red) at time t_2 (pH about 8), indicating a semi-solid state; and a yellow color (mixture of yellow and yellow) at time t_3 (pH about 8), indicating a solid state.

As another example (in which lower pH values can be differentiated), phenolphthalein or o-cresolphthalein exhibit a red color at pH 9-10 and exhibit are clear color (i.e., are "colorless") at pH 8 and below. Bromothymol blue exhibits a blue color at pH 7 and above, and a yellow color at pH 6 and below. By including a mixture of phenolphthalein (or o-cresolphthalein) and bromothymol blue, the composition, as it cross-links, will exhibit a purple/reddish color (mixture of purple and red) when the pH is greater than 9, indicating a liquid state; a blue color (mixture of clear and blue) when the pH is about 8), indicating a semi-solid state; and a yellow color (mixture of clear and yellow) when the pH is about 6-7, indicating a solid state.

B. Controlling the Rate of Degradation

The rate of degradation is controlled by the degradation control region (DCR), the concentration of the CG's in the polymer solution, and the concentration

of the nucleophilic groups in the protein solution. Changes in these concentrations also typically result in changes in the mechanical properties of the hydrogel, as well as the rate of degradation.

The rate of degradation is best controlled by the selection of the chemical moiety in the degradation control region, DCR. If degradation is not desired, a DCR can be selected to prevent biodegradation or the material can be created without a DCR. However, if degradation is desired, a hydrolytically or enzymatically degradable DCR can be selected. Examples of hydrolytically degradable moieties include saturated di-acids, unsaturated di-acids, poly(glycolic acid), poly(DL-lactic acid), poly(L-lactic acid),poly(ξ-caprolactone), poly(δ-valerolactone),poly(γ-butyrolactone), poly(amino acids),poly(anhydrides), poly(orthoesters), poly(orthocarbonates), and poly(phosphoesters). Examples of enzymatically degradable DCR's include Leu-Gly-Pro-Ala (collagenase sensitive linkage) and Gly-Pro-Lys (plasmin sensitive linkage). It should also be appreciated that the DCR could contain combinations of degradable groups, e.g. poly(glycolic acid) and di-acid.

Through the selection of the DCR, the transformation of the material from a solid hydrogel to a degraded liquid can be controlled from as little as 1 day to greater than 500 days, more preferably 5 days to 30 days.

C. Controlling the Mechanical Properties

Desired mechanical properties of the hydrogel include cohesive strength, adhesive strength, and elasticity. Through the selection of the functionality, concentration, and molecular weight of the protein and polymer, the mechanical properties of the hydrogel can be adjusted to suit a variety of clinical needs.

The mechanical properties of the hydrogel are

controlled, in part, by the number of crosslinks in the hydrogel network as well as the distance between crosslinks. Both the number of crosslinks and the distance between crosslinks are dependent on the functionality, concentration, and molecular weight of the polymer and the protein.

Functionality, or the number of reactive groups per molecule, affects the mechanical properties of the resulting hydrogel by influencing both the number of and distance between crosslinks. As discussed previously, the utility of a given polymer significantly increases when the functionality is increased to be greater than or equal to three. The observed incremental increase in functionality occurs when the functionality is increased from two to three, and again when the functionality is increased from three to four. By increasing the functionality of the polymer or protein at a constant concentration, the concentration of crosslinking groups available for reaction are increased and more crosslinks are formed. However, increased mechanical properties cannot be controlled with functionality alone. Ultimately, the steric hindrances of the protein or polymer to which the reactive groups are attached predominate and further changes in the mechanical properties of the hydrogel are not observed. The effect of functionality is saturated when the functionality reaches about four.

The concentration of the protein and polymer also affect the mechanical properties of the resulting hydrogel by influencing both the number of and distance between crosslinks. Increasing the protein and polymer concentration increases the number of available crosslinking groups, thereby increasing the strength of the hydrogel. However, decreases in the elasticity of the hydrogel are observed as the concentration of the

protein and polymer is increased. The effects on the mechanical properties by concentration are limited by the solubility of the protein and polymer.

The polymer and protein molecular weight affects the mechanical properties of the resulting hydrogel by influencing both the number of and distance between crosslinks. Increasing the molecular weight of the protein and polymer decreases the number of available crosslinking groups, thereby decreasing the strength of the hydrogel. However, increases in the elasticity of the hydrogel are observed with increasing molecular weight of the protein and polymer. Low molecular weight proteins and polymers result in hydrogels that are strong, but brittle. Higher molecular weight proteins and polymers result in weaker, but more elastic gels. The effects on the mechanical properties by molecular weight are limited by the solubility of the protein and polymer. However, consideration to the ability of the body to eliminate the polymer should be made, as large molecular weight polymers are difficult to clear.

IV. Exemplary Species Compositions

It should be appreciated that by adjusting the rate of gelation, the mechanical properties of the resulting hydrogel, and the rate of degradation, the genus material composition can be adapted for use in a variety of medical indications.

The following species compositions and their therapeutic indications are included by way of example.

A. Species 1: Sealing of Vascular Puncture Sites

For sealing vascular puncture sites, a biomaterial formulation with a gelation time of fifteen to sixty seconds is preferred, more preferably fifteen to thirty seconds. This period allows the biomaterial to be delivered through the delivery device and flow into the

surface irregularities before solidification. The period before solidification also enhances patient safety when compared to alternatives in the prior art.

Collagen plugs or slurries have been previously used to seal vascular puncture sites. However, if the collagen plug or slurry enters the vasculature, emboli downstream from the arteriotomy is a distinct possibility. In contrast, preclinical studies have demonstrated that emboli do not form if the a biomaterial of the Species 1 enters the bloodstream before solidification. Biomaterial of the Species 1 is diluted in flowing blood to a point where emboli cannot be formed. Furthermore, the rate of gelation is reduced at the pH of flowing blood, further enhancing the dilution effect.

For this indication, the hydrogel Species 1 possesses sufficient adhesive strength to prevent dislodging from the arteriotomy. The hydrogel Species 1 also has sufficient cohesive strength to prevent rupture under arterial pressure, i.e., up to about 200 mm Hg. The hydrogel Species 1 also seals the arteriotomy for up to 15 days post-application before loss of mechanical properties through degradation, and completely degrades by 30 days post-application.

The following is a representative composition for Species 1:

Polymer component: 17% w/w 4-arm poly(ethylene glycol) tetra-succinimidyl glutarate, MW 10,000 in water for injection.

Protein component: 25% w/w human serum albumin, USP supplemented with 300 mM dibasic sodium phosphate, USP.

B. Species 2: Sealing Tissue from Blood Leaks

Preclinical studies have demonstrated that a biomaterial of Species 2 is effective in controlling diffuse organ bleeding. The bleeding is not controlled

via physiological interactions with the clotting cascade, but rather the biomaterial of Species 2 mechanically seals the tissue to control the bleeding.

For this indication, the biomaterial formulation of the Species 2 possesses an instantaneous gelation time. To achieve hemostasis in this indication, the biomaterial Species 2 solidifies before being removed from the site by gravity and/or diluted by flowing blood. The resulting hydrogel Species 2 also possesses sufficient adhesive strength to prevent dislodging from the wound and sufficient cohesive strength to prevent rupture under arterial pressure, up to about 200 mm Hg. The hydrogel Species 2 seals the wound for up to 15 days post-application before loss of mechanical properties through degradation, and completely degrades by 30 days post-application.

The following is a representative composition for Species 2:

Polymer component: 17% w/w 4-arm poly(ethylene glycol) tetra-succinimidyl succinate, MW 10,000 in water for injection.

Protein component: 25% w/w human serum albumin, USP supplemented with 250 mM sodium carbonate and 50 mM sodium bicarbonate.

C. Species 3: Sealing Tissue from Gas Leaks

Preclinical studies have demonstrated that Species 3 is effective in controlling air leaks from the lung. The biomaterial of Species 3 forms a mechanical barrier over the suture or staple line.

In this indication, the biomaterial of Species 3 possesses an instantaneous gelation time. To achieve sealing in this indication, the biomaterial solidifies before being removed from the site by gravity. The resulting hydrogel Species 3 possesses sufficient adhesive strength to prevent dislodging from the wound

and sufficient cohesive strength to prevent rupture under physiological lung pressure. Hydrogel Species 3 also exhibits sufficient elasticity to withstand repeated lung inflation. The hydrogel Species 3 seals the wound for up to 15 days post-application before loss of mechanical properties through degradation, and completely degrades by 30 days post-application.

The following is a representative composition for Species 3:

Polymer component: 17% w/w 4-arm poly(ethylene glycol) tetra-succinimidyl succinate, MW 10,000 in water for injection.

Protein component: 25% w/w human serum albumin, USP supplemented with 250 mM sodium carbonate and 50 mM sodium bicarbonate.

D. Species 4: Sealing Tissue from Liquid Leaks

To seal a liquid leak, the biomaterial of Species 4 forms a mechanical barrier over the wound, suture, or staple line. The biomaterial of Species 4 possesses an instantaneous gelation time, to solidify before being removed from the site by gravity. The resulting hydrogel Species 4 exhibits sufficient adhesive strength to prevent dislodging from the wound and sufficient cohesive strength to prevent rupture under physiological pressure. The hydrogel Species 4 seals for up to 15 days post-application before loss of mechanical properties through degradation and completely degrades by 30 days post-application.

The following is a representative composition for Species 4:

Polymer component: 17% w/w 4-arm poly(ethylene glycol) tetra-succinimidyl succinate, MW 10,000 in water for injection.

Protein component: 25% w/w human serum albumin, USP supplemented with 250 mM sodium carbonate and 50 mM

sodium bicarbonate.

E. Species 5: Sealing Tissue from Solid Leaks

To seal a solid leak, the biomaterial of Species 5 forms a mechanical barrier over the wound, suture, or staple line. The biomaterial of Species 5 has an instantaneous gelation time, to solidify before being removed from the site by gravity.

The resulting hydrogel Species 5 has sufficient adhesive strength to prevent dislodging from the wound and sufficient cohesive strength to prevent rupture under physiological pressure. The hydrogel Species 5 seals the wound for up to 15 days post-application before loss of mechanical properties through degradation, and is completely degraded by 30 days post-application.

The following is a representative composition for Species 5:

Polymer component: 17% w/w 4-arm poly(ethylene glycol) tetra-succinimidyl succinate, MW 10,000 in water for injection.

Protein component: 25% w/w human serum albumin, USP supplemented with 250 mM sodium carbonate and 50 mM sodium bicarbonate.

F. Species 6: Prevention of Post-Operative Adhesions

The biomaterial of Species 6 coats the injured tissue surface, preventing the deposition of fibrin, and allows the formation of a new layer of epithelial cells. For the prevention of post-operative adhesions, the biomaterial of Species 6 is capable of being laparoscopically delivered, and possesses an instantaneous gelation time. For this indication, the biomaterial Species 6 solidifies before being removed from the site by gravity.

The resulting hydrogel Species 6 has sufficient adhesive strength to prevent dislodging from the wound.

The hydrogel Species 6 adheres to the tissue for three to fifteen days post-application, preferably seven to ten days, before significant amounts of degradation occur. The biomaterial of Species 6 completely degrades in five to 180 days post-application, preferably five to thirty days.

The following is a representative composition for Species 6:

Polymer component: 9% w/w 4-arm poly(ethylene glycol) tetra-succinimidyl succinate, MW 10,000 in water for injection.

Protein component: 13% w/w human serum albumin, USP supplemented with 250 mM sodium carbonate and 50 mM sodium bicarbonate.

G. Species 7: Repair of Tissue Voids

The biomaterial of Species 7 fills the tissue void and solidifies. For repair of tissue voids, a biomaterial of Species 7 possesses a gelation time of approximately 5 seconds. The five second gelation time allows the formulation to enter the void, fill surface irregularities, achieve hemostasis, and prevent the formation of air pockets inside the hydrogel. The resulting hydrogel Species 7 has sufficient adhesive strength to prevent dislodging from the void and sufficient cohesive strength to prevent rupture under venous pressure, up to 100 mm Hg. The hydrogel Species 7 seals the wound for up to 15 days post-application before loss of mechanical properties through degradation and completely degraded by 30 to 60 days post-application.

The following is a representative composition for Species 7:

Polymer component: 17% w/w 4-arm poly(ethylene glycol) tetra-succinimidyl glutarate, MW 10,000 in water for injection.

Protein component: 25% w/w human serum albumin, USP supplemented with 100 mM sodium carbonate and 50 mM sodium bicarbonate.

H. Species 8: Augmentation of Tissue

The biomaterial of Species 8 enhances the desired tissue and solidifies. For tissue augmentation, the biomaterial of Species 8 has a gelation time of approximately 120 seconds, to allow the formulation to enter the surface irregularities, to prevent the formation of air pockets inside the hydrogel, and to allow the user to add or subtract volume to achieve the desired effect.

The resulting hydrogel Species 8 has sufficient adhesive strength to prevent dislodging from the tissue site. The hydrogel Species 8 does not degrade for up to one year post-application.

The following is a representative composition for Species 8:

Polymer component: 17% w/w 4-arm poly(ethylene glycol) tetra-propionic acid succinimidyl ester, MW 10,000 in water for injection.

Protein component: 25% w/w human serum albumin, USP

I. Species 9: Embolization of Arterio-Venous Malformations (AVM's)

The biomaterial of Species 9 is delivered as a liquid, but quickly sets up to a solid, embolizing the AVM. For embolization of AVM's, the biomaterial of Species 9 has a gelation time of approximately 30 to 120 seconds. The time before solidification allows the biomaterial of Species 9 to fill the tortuous mass of blood vessels completely.

The resulting hydrogel Species 9 has sufficient adhesive strength to prevent dislodging from the tissue site. The degradation of the hydrogel Species 9 is not relevant, as the AVM is removed immediately after

embolization.

The following is a representative composition for Species 9:

Polymer component: 17% w/w 4-arm poly(ethylene glycol) tetra-succinimidyl glutarate, MW 10,000 in water for injection.

Protein component: 25% w/w human serum albumin

J. Species 10: Filling of Aneurysms

The biomaterial of Species 10 is delivered as a liquid, but quickly sets up to a solid to fill the aneurysm. For aneurysm filling, the biomaterial of Species 10 exhibits a gelation time of approximately 5 to 30 seconds. The time before solidification allows the formulation to fill the aneurysm completely.

The resulting hydrogel Species 10 has sufficient adhesive strength to prevent dislodging from the aneurysm and sufficient cohesive strength to prevent rupture under arterial pressure, up to about 200 mm Hg. The hydrogel Species 10 does not degrade for up to one year post-application.

The following is a representative composition for Species 10:

Polymer component: 17% w/w 4-arm poly(ethylene glycol) tetra-propionic acid succinimidyl ester, MW 10,000 in water for injection.

Protein component: 25% w/w human serum albumin, USP supplemented with 100 mM sodium carbonate and 50 mM sodium bicarbonate.

K. Species 11: Delivery of Pharmaceuticals

The biomaterial of Species 11 serves as the depot for the pharmaceutical or vector. The resulting hydrogel Species 11 can be solidified directly on the diseased tissue. For delivery of pharmaceuticals, a biomaterial of Species 11 has a gelation time of approximately 5 to 30 seconds. The resulting hydrogel Species 11 has

sufficient adhesive strength to prevent dislodging from the tissue and sufficient cohesive strength to prevent fragmentation. The degradation of the hydrogel Species 11 is dependent on the desired time frame for release of the pharmaceutical, ranging from 1 week to 1 year.

The following is a representative composition for Species 11:

Polymer component: 17% w/w 4-arm poly(ethylene glycol) tetra-succinimidyl glutarate, MW 10,000 in water for injection.

Protein component: 25% w/w human serum albumin supplemented with 75 mM sodium carbonate and 75 mM sodium bicarbonate.

L. Species 12: Delivery of Cells

The biomaterial of Species 12 serves as the matrix for the cells to be delivered. For delivery of cells, the biomaterial of Species 12 has a gelation time of approximately 5 to 30 seconds.

The resulting hydrogel Species 12 has sufficient adhesive strength to prevent dislodging from the tissue and sufficient cohesive strength to prevent fragmentation. The degradation of the hydrogel Species 12 is dependent on the desired time frame for the cells to remodel the tissue, ranging from 1 week to 6 months.

The following is a representative composition for Species 12:

Polymer component: 17% w/w 4-arm poly(ethylene glycol) tetra-succinimidyl glutarate, MW 10,000 in water for injection.

Protein component: 25% w/w human serum albumin supplemented with 75 mM sodium carbonate and 75 mM sodium bicarbonate.

The following Table summarizes the gelation time, degradation time, and mechanical properties of the species 1 to 12 the composition genus 10.

Table 2

Principal Characteristics and Therapeutic Indications of Species 1 to 12 of the Fundamental Genus Composition

Species	Gelation Time	Degradation Time	Mechanical Properties	Therapeutic Indication
1	15 to 60 Seconds	30 Days	Adhesive Strength: Prevent Dislodgment Cohesive Strength: Prevent Rupture Under Arterial Pressure	Sealing of Vascular Puncture Sites
2	Instan-taneous	30 Days	Adhesive Strength: Prevent Dislodgment Cohesive Strength: Prevent Rupture Under Arterial Pressure	Sealing Tissue from Blood Leaks

Species	Gelation Time	Degradation Time	Mechanical Properties	Therapeutic Indication
3	Instan-taneous	30 days	Adhesive Strength: Prevent Dislodgment Cohesive Strength: Prevent Rupture under Lung Pressure Elasticity: To Withstand Repeated Lung Inflation	Sealing Tissue from Gas Leaks
4	Instan-taneous	30 days	Adhesive Strength: Prevent Dislodgment Cohesive Strength: Prevent Rupture under Physiologic Pressure	Sealing Tissue from Liquid Leaks

Species	Gelation Time	Degradation Time	Mechanical Properties	Therapeutic Indication
5	Instan-taneous	30 days	Adhesive Strength: Prevent Dislodgment Cohesive Strength: Prevent Rupture under Physiologic Pressure	Sealing Tissue from Solid Leaks
6	Instan-taneous	5 to 30 Days	Adhesive Strength: Prevent Dislodgment	Prevention of Post Operative Adhesions
7	5 Seconds	30 to 60 Days	Adhesive Strength: Prevent Dislodgment Cohesive Strength: Prevent Rupture under Venous Pressure	Repair of Tissue Voids
8	120 seconds	1 Year	Adhesive Strength: Prevent Dislodgment	Augmentation of Tissue

Species	Gelation Time	Degradation Time	Mechanical Properties	Therapeutic Indication
9	30 to 120 seconds	N/A	Adhesive Strength: Prevent Dislodgment	Embolization of AVM's
10	5 to 30 Seconds	1 Year	Adhesive Strength: Prevent Dislodgment Cohesive Strength: Prevent Rupture Under Arterial Pressure	Filling of Aneurysms
11	5 to 30 Seconds	1 Year	Adhesive Strength: Prevent Dislodgment Cohesive Strength: Prevent Fragmenta-tion	Delivery of Pharmaceu-ticals

Species	Gelation Time	Degradation Time	Mechanical Properties	Therapeutic Indication
12	5 to 30 seconds	1 week to 6 months	Adhesive Strength: Prevent Dislodgment Cohesive Strength: Prevent Fragmenta-tion	Delivery of Cells

VI. General Methodology for Species Development

Fig. 5 shows a flowchart illustrating a methodology 200 for developing species compositions based upon the composition genus 10.

The first step 202 is to select a desired clinical indication. Based upon the therapeutic requirements of the selected clinical indication, steps 204, 206, and 208 are followed to identify, respectively, the mechanical properties, the rate of gelation, and the rate of degradation suited for the indication.

Upon identifying the mechanical properties desired for the indication, a step 210 is carried out to selectively select the components of the composition genus 10, so as to create a species having the desired mechanical properties. As discussed previously, the mechanical properties can be selected through the concentration of the protein and the polymer. Elasticity can be obtained through lower concentrations of the protein and the polymer and increasing molecular weight of the polymer. Cohesive strength can be obtained through higher concentrations of the protein and the polymer and decreasing molecular weight of the polymer. Increased adhesive strength can be obtained by increasing

the ratio of the concentration of polymer to the concentration of the protein. Until the buffer system is fully optimized, the evaluation of the mechanical properties at this step 210 should be performed after a suitable cross-linking period, to allow completion of the crosslinking reaction.

Once the desired mechanical properties have been achieved, a step 212 can be carried out to further selectively tailor the components of the composition genus 10 to create for the species the desired rate of gelation. As discussed previously, the rate of gelation can be selected with the buffer system and the cross-linking group of the polymer. Increased rates of gelation can be achieved by using carbonate buffers, higher pH's, and higher buffer concentrations. Decreased rates of gelation can be achieved by using phosphate buffers, lower pH's, and lower buffer concentrations. Once the desired rate of gelation has been obtained, it should be verified that the desired mechanical properties are still present during the clinically relevant period.

Once the desired mechanical properties and rate of gelation have been achieved, a step 214 can be carried out to further selectively tailor the components of the composition genus 10 to create for the species the desired rate of degradation. As discussed previously, the rate of degradation can be selected by changing the degradation control region on the polymer portion of the genus composition. Increased rates of degradation can be achieved by using glycolide or lactide, while decreased rates of degradation can be achieved by using glutaric acid as the degradation control region. A formulation that does not degrade can also be achieved by elimination of the degradation control region. Once the desired rate of degradation has been obtained, it should be verified that the desired mechanical properties and rate of

gelation are still maintained.

A step 216 can now be conducted to evaluate the species in *in vitro* models, if available. These models are used to verify the mechanical properties and rate of gelation in a clinically relevant manner. If the results indicate that these properties need to be adjusted, they can be refined.

A final step 218 comprises *in vivo* experimentation. In the *in vivo* experimentation, the biocompatibility, effectiveness, and rate of degradation of the species are confirmed.

VII. Exemplary Delivery Systems

The delivery systems 14 serve to mix the fundamental protein and polymer solution components intimately, using atomization, static mixers, or in-line channel mixing. The mixing technique employed depends upon the requirements of the particular therapeutic indication, and, in particular, the gelation time and morphology of the treatment site.

A typical delivery system 14 for the genus material composition (see Fig. 3) includes, in the first kit 16, first and second dispensing syringes 60 and 62, in which the formative components of the genus material composition are contained.

The first dispensing syringe 60 contains a concentration of buffered protein solution component 100. The protein solution is supplemented with the appropriate buffers, sterile filtered, aseptically filled into the syringe 60, and the syringe 60 is capped for storage prior to use.

The second dispensing syringe 62 contains an inert, electrophilic, water soluble polymer component 102. The polymer component 102 is initially packaged prior to use in the second dispensing syringe 62 in an inert

atmosphere (e.g., argon) in a stable, powder form.

In this arrangement, the first kit 16 includes a third syringe 104, which contains sterile water 106 for dissolution of the powder polymer 102 just before mixing with the albumin component 100. In facilitating mixing, a stopcock valve 108 is secured to the luer fitting 88 at the dispensing end of the second dispensing syringe 62. The dispensing end 110 of the water syringe 104 couples to the stopcock valve 108, so that the water 106 can be mixed with the polymer 102 in the dispensing syringe 62 prior to use.

As Fig. 3 also shows, the second kit 18 carries the material introducer/mixer 22. As Fig, 4 shows, the two dispensing syringes 60 and 62 are snap-mounted on the material introducer/mixer 22. The material introducer/mixer 22 includes a joiner 84. The joiner 84 includes side by side female luer fittings 86. The female luer fittings 86 each receives the threaded male luer fitting 88 at the dispensing end of the dispensing syringes 60 and 62.

The joiner 84 includes interior channels 90 coupled to the female luer fittings 86. The channels 90 merge at a Y-junction into a single outlet port 92. The joiner 84 maintains two fluids dispensed by the syringes 60 and 62 separately until they leave the joiner 84. This design minimizes plugging of the joiner 84 due to a mixing reaction between the two fluids. A syringe clip 68 can be provided to ensure even application of individual solutions through the joiner 84.

The parts of the introducer/mixer 22 and joiner are made, e.g., by molding medical grade plastic materials, such as polycarbonate and acrylic.

For those therapeutic indications where the species composition needs to undergo instantaneous gelation, or gelation within a matter of a few seconds, and where the

application site is exposed (e.g., Species 2, 3, 4, 5, 6, 7, 8, 9), the material introducer/mixer 22 can include a mixing spray head 94 coupled to the joiner (see Fig. 4). Preferably, the kit contains several interchangeable mixing spray heads 94, in case one mixing spray head 94 becomes clogged during use.

The mixing spray head 94 may be variously constructed and comprise a conventional spray head.

Alternatively, the material introducer/mixer 22 can include a cannula 152, which, in use, can be coupled to the joiner.

For those therapeutic indications where the species composition needs to undergo a longer period of gelation, and where access is required to a subsurface tissue site (e.g., Species 1 and 10),the material introducer/mixer 22 can include a catheter tube assembly 26 (see Fig. 3) that couples to the joiner 84. The catheter tube assembly 24 includes, at its distal end, a circumferentially spaced array of nozzles 34. The barrier material is conveyed in liquid form and dispensed in a circumferential manner through the nozzles 34 at the puncture site.

Expressed in tandem from the dispensing syringes 60 and 62, which are mechanically linked together by the joiner 84, the two fundamental components of the genus material composition come into contact in the liquid state either in the mixing spray head 94, or the cannula 152, or in the catheter tube assembly 26. Atomization of the two components occurs as they are dispersed through the mixing spray head 94. Passage of the liquid components through the cannula 152 or catheter tube will channel-mix the materials. Either by atomization or channel mixing, the liquid components are sufficiently mixed to immediately initiate the cross-linking reaction.

The material introducer/mixer 22 allows the physician to uniformly dispense the two components in a

liquid state from the dispensing syringes 60 and 62. The material introducer/mixer 22 also mixes the components while flowing in the liquid state from the dispensing syringes 60 and 62.

Further details of delivery systems for those species applied by spraying on exposed tissue sites are found in copending United States Patent Application Serial No. 09/283,535, filed April 1, 1999, and entitled "Compositions, Systems, And Methods For Arresting or Controlling Bleeding or Fluid Leakage in Body Tissue," which is incorporated herein by reference.

Further details of delivery systems for those species introduced by catheter-based systems are found in copending United States Patent Application Serial No. 09/188,083, filed November 6, 1998 and entitled "Compositions, Systems, and Methods for Creating in Situ, Chemically Cross-linked, Mechanical Barriers," which is likewise incorporated herein by reference. For example, when used to deliver the Species 1 material composition, a 5.5 Fr catheter tube can be used to seal arteriotomies from 5 Fr to 10 Fr, without filling the tissue track with the Species 1 material composition. The Species 1 material composition is delivered adjacent to the arteriotomy, while the delivery device prevents the liquid from filling the tissue track. This feature ensures that the Species 1 material composition remains at the arteriotomy for maximum efficacy.

The features of the invention are set forth in the following claims.

We Claim:

1. A biocompatible material comprising a mixture of a protein solution and a polymer solution including a derivative of a hydrophilic polymer with a functionality of at least three, wherein, upon mixing, the protein solution and the polymer solution cross-link to form a non-liquid, three-dimensional network that degrades over time back to a liquid form, the polymer including a degradation control region selected to achieve a desired degradation period.

2. A material according to claim 1

wherein the degradation control region is selected to achieve a desired degradation period within a range of between about 1 day to greater than 500 days.

3. A material according to claim 1

wherein the degradation control region is selected to achieve a desired degradation period within a range of between about 5 days to about 30 days.

4. A material according to claim 1

wherein the degradation control region comprises at least one selectable hydrolytically degradable moiety.

5. A material according to claim 4

wherein the hydrolytically degradable moiety includes saturated di-acids, unsaturated di-acids, poly(glycolic acid), poly(DL-lactic acid), poly(L-lactic acid), poly(ξ-caprolactone), poly(δ-valerolactone), poly(γ-butyrolactone), poly(amino acids), poly(anhydrides), poly(orthoesters), poly(orthocarbonates), or poly(phosphoesters).

6. A material according to claim 1

wherein the degradation control region comprises at least one selectable enzymatically degradable moiety.

7. A material according to claim 6

wherein the enzymatically degradable moiety includes Leu-Glyc-Pro-Ala (collagenes sensitive linkage)

or Gly-Pro-Lys (plasmin sensitive linkage).

8. A biocompatible material comprising a mixture of a protein solution and a polymer solution including a derivative of a hydrophilic polymer with a functionality of at least three, wherein, upon mixing, the protein solution and the polymer solution cross-link over time to form a non-liquid, three-dimensional network, the polymer including a cross-linking group selected to achieve a desired cross-linking period.

9. A material according to claim 8

wherein the cross-linking group is selected to achieve a desired cross-linking period within a range of from less than one second to greater than 10 hours.

10. A material according to claim 8

wherein the cross-linking group is selected to achieve a desired cross-linking period within a range of from less than one second to about 10 minutes.

11. A material according to claim 8

wherein the cross-linking group is selected to achieve a desired cross-linking period within a range from less than 1 second to about 2 minutes.

12. A material according to claim 8

wherein the cross-linking group is selected to react with at least one thiol.

13. A material according to claim 8

wherein the cross-linking group is selected from a group consisting essentially of vinyl sulfone, N-ethyl maleimide, iodoacetamide, and orthopyridyl disulfide.

14. A material according to claim 8

wherein the cross-linking group is selected to react with at least one amine.

15. A material according to claim 8

wherein the cross-linking group is selected from a group consisting essentially of aldehydes.

16. A material according to claim 8

wherein the cross-linking group is selected from a group consisting essentially of active esters, epoxides, oxycarbonylimidazole, nitrophenyl carbonates, tresylate, mesylate, tosylate, and isocyanate.

17. A material according to claim 8 wherein the cross-linking group includes an ester of N-hydroxysuccinimide.

18. A material according to claim 8

wherein the protein solution includes a buffer.

19. A material according to claim 18

wherein the buffer includes carbonate or phosphate.

20. A material according to claim 1 or 8

wherein the polymer comprises a compound of the formula PEG-$(DCR-CG)_n$, where PEG is poly(ethylene glycol), DCR is the degradation control region, CG is the cross-linking group, and n is equal to or greater than three.

21. A material according to claim 20

wherein the compound comprises a multi-armed polymer structure.

22. A material according to claim 1 or 8

wherein the protein solution comprises at least one non-immunogenic, hydrophilic protein.

23. A material according to claim 22

wherein the non-immunogenic, hydrophilic protein is selected from a group consisting essentially of serum, serum fractions, and solutions of albumin, gelatin, antibodies, fibrinogen, and serum proteins.

24. A material according to claim 1 or 8

wherein the protein solution comprises at least one water soluble derivative of a hydrophobic protein.

25. A material according to claim 24

wherein the water soluble derivative of a hydrophobic protein is selected from a group consisting essentially of comprising solutions of collagen, elastin,

chitosan, and hyaluronic acid.

26. A material according to claim 1 or 8

wherein the protein solution comprises at least one hybrid protein.

27. A material according to claim 1 or 8

wherein the protein solution comprises at least one synthetic amino acid sequence.

28. A material according to claim 1 or 8

wherein the protein solution comprises recombinant or natural human serum albumin.

29. A material according to claim 28

wherein the human serum albumin is at a concentration of about 25% or less.

30. A material according to claim 1 or 8

wherein the polymer solution includes a derivative of a polymer selected from a group consisting essentially of poly(ethylene glycol), poly(ethylene oxide), poly(vinyl alcohol), poly(vinylpyrrolidone), poly(ethyloxazoline), poly(ethylene glycol)-co-poly(propylene glycol) block copolymers, or electrophilically derivatized polysaccharides, carbohydrates, or proteins.

31. A material according to claim 1 or 8

wherein the polymer solution comprises at least one hybrid protein.

32. A material according to claim 1 or 8

wherein the polymer solution comprises at least one synthetic amino acid sequence.

33. A material according to claim 1 or 8

wherein the polymer is comprised of poly(ethylene glycol)(PEG).

34. A material according to claim 33

wherein the PEG has a molecular weight of between about 1,000 and about 30,000 g/mole.

35. A material according to claim 33

wherein the PEG has a molecular weight of between about 2,000 and about 15,000 g/mole.

36. A material according to claim 33

wherein the PEG has a molecular weight of between about 10,000 and 15,000 g/mole.

37. A material according to claim 33

wherein the PEG comprises a multi-armed polymer structure.

38. A biocompatible material comprising a mixture of a protein solution and a polymer solution including a derivative of a hydrophilic polymer with a functionality of at least three, wherein, upon mixing, the protein solution and the polymer solution cross-link over time to form a non-liquid, three-dimensional network that degrades over time back to a liquid form, the polymer including a degradation control region selected to achieve a desired degradation period, the polymer also including a cross-linking group selected to achieve a desired cross-linking period.

39. A material according to claim 38

wherein the degradation control region is selected to achieve a desired degradation period within a range of between about 1 day to greater than 500 days.

40. A material according to claim 38

wherein the degradation control region is selected to achieve a desired degradation period within a range of between about 5 days to about 30 days.

41. A material according to claim 38

wherein the cross-linking group is selected to achieve a desired cross-linking period within a range of from less than one second to greater than 10 hours.

42. A material according to claim 38

wherein the cross-linking group is selected to achieve a desired cross-linking period within a range of from less than one second to about 10 minutes.

43. A material according to claim 38

wherein the cross-linking group is selected to achieve a desired cross-linking period within a range from less than 1 second to about 2 minutes.

44. A system for forming a biocompatible material comprising

a protein solution,

a polymer solution including a derivative of a hydrophilic polymer with a functionality of at least three, wherein, upon mixing, the protein solution and the polymer solution cross-link to form a non-liquid, three-dimensional network that degrades over time back to a liquid form, the polymer including a degradation control region selected to achieve a desired degradation period, the polymer also including a cross-linking group selected to achieve a desired cross-linking period, and

instructions for forming a mixture of the protein solution and polymer solution and for applying the mixture to seal a vascular puncture site.

45. A system according to claim 44

wherein the degradation control region is selected to achieve a desired degradation period of approximately 30 days.

46. A system according to claim 44 or 45

wherein the cross-linking group is selected to achieve a desired cross-linking period within a range of about 15 to 60 seconds.

47. A system for forming a biocompatible material comprising

a protein solution,

a polymer solution including a derivative of a hydrophilic polymer with a functionality of at least three, wherein, upon mixing, the protein solution and the polymer solution cross-link to form a non-liquid, three-dimensional network that degrades over time back to a

liquid form, the polymer including a degradation control region selected to achieve a desired degradation period, the polymer also including a cross-linking group selected to achieve a desired cross-linking period, and

instructions for forming a mixture of the protein solution and polymer solution and for applying the mixture to seal tissue from blood leaks.

48. A system according to claim 47

wherein the degradation control region is selected to achieve a desired degradation period of approximately 30 days.

49. A system according to claim 47 or 48

wherein the cross-linking group is selected to achieve a desired cross-linking period of less than one second.

50. A system for forming a biocompatible material comprising

a protein solution,

a polymer solution including a derivative of a hydrophilic polymer with a functionality of at least three, wherein, upon mixing, the protein solution and the polymer solution cross-link to form a non-liquid, three-dimensional network that degrades over time back to a liquid form, the polymer including a degradation control region selected to achieve a desired degradation period, the polymer also including a cross-linking group selected to achieve a desired cross-linking period, and

instructions for forming a mixture of the protein solution and polymer solution and for applying the mixture to seal tissue from gas leaks.

51. A system according to claim 50

wherein the degradation control region is selected to achieve a desired degradation period of approximately 30 days.

52. A system according to claim 50 or 51

wherein the cross-linking group is selected to achieve a desired cross-linking period of less than one second.

53. A system for forming a biocompatible material comprising

a protein solution,

a polymer solution including a derivative of a hydrophilic polymer with a functionality of at least three, wherein, upon mixing, the protein solution and the polymer solution cross-link to form a non-liquid, three-dimensional network that degrades over time back to a liquid form, the polymer including a degradation control region selected to achieve a desired degradation period, the polymer also including a cross-linking group selected to achieve a desired cross-linking period, and

instructions for forming a mixture of the protein solution and polymer solution and for applying the mixture to seal tissue from liquid leaks.

54. A system according to claim 53

wherein the degradation control region is selected to achieve a desired degradation period of approximately 30 days.

55. A system according to claim 53 or 54

wherein the cross-linking group is selected to achieve a desired cross-linking period of less than one second.

56. A system for forming a biocompatible material comprising

a protein solution,

a polymer solution including a derivative of a hydrophilic polymer with a functionality of at least three, wherein, upon mixing, the protein solution and the polymer solution cross-link to form a non-liquid, three-dimensional network that degrades over time back to a liquid form, the polymer including a degradation control

region selected to achieve a desired degradation period, the polymer also including a cross-linking group selected to achieve a desired cross-linking period, and

instructions for forming a mixture of the protein solution and polymer solution and for applying the mixture to seal tissue from solid leaks.

57. A system according to claim 56

wherein the degradation control region is selected to achieve a desired degradation period of approximately 30 days.

58. A system according to claim 56 or 57

wherein the cross-linking group is selected to achieve a desired cross-linking period of less than one second.

59. A system for forming a biocompatible material comprising

a protein solution,

a polymer solution including a derivative of a hydrophilic polymer with a functionality of at least three, wherein, upon mixing, the protein solution and the polymer solution cross-link to form a non-liquid, three-dimensional network that degrades over time back to a liquid form, the polymer including a degradation control region selected to achieve a desired degradation period, the polymer also including a cross-linking group selected to achieve a desired cross-linking period, and

instructions for forming a mixture of the protein solution and polymer solution and for applying the mixture to prevent post-operative adhesions.

60. A system according to claim 59

wherein the degradation control region is selected to achieve a desired degradation period within a range of approximately 5 to 30 days.

61. A system according to claim 59 or 60

wherein the cross-linking group is selected to

achieve a desired cross-linking period of less than one second.

62. A system for forming a biocompatible material comprising

a protein solution,

a polymer solution including a derivative of a hydrophilic polymer with a functionality of at least three, wherein, upon mixing, the protein solution and the polymer solution cross-link to form a non-liquid, three-dimensional network that degrades over time back to a liquid form, the polymer including a degradation control region selected to achieve a desired degradation period, the polymer also including a cross-linking group selected to achieve a desired cross-linking period, and

instructions for forming a mixture of the protein solution and polymer solution and for applying the mixture to repair a tissue void.

63. A system according to claim 62

wherein the degradation control region is selected to achieve a desired degradation period in a range of approximately 30 to 60 days.

64. A system according to claim 62 or 63

wherein the cross-linking group is selected to achieve a desired cross-linking period of approximately 5 seconds.

65. A system for forming a biocompatible material comprising

a protein solution,

a polymer solution including a derivative of a hydrophilic polymer with a functionality of at least three, wherein, upon mixing, the protein solution and the polymer solution cross-link to form a non-liquid, three-dimensional network that degrades over time back to a liquid form, the polymer including a degradation control region selected to achieve a desired degradation period,

the polymer also including a cross-linking group selected to achieve a desired cross-linking period, and

instructions for forming a mixture of the protein solution and polymer solution and for applying the mixture to augment tissue.

66. A system according to claim 65

wherein the degradation control region is selected to achieve a desired degradation period of approximately one year.

67. A system according to claim 65 or 66

wherein the cross-linking group is selected to achieve a desired cross-linking period of approximately 120 seconds.

68. A system for forming a biocompatible material comprising

a protein solution,

a polymer solution including a derivative of a hydrophilic polymer with a functionality of at least three, wherein, upon mixing, the protein solution and the polymer solution cross-link to form a non-liquid, three-dimensional network that degrades over time back to a liquid form, the polymer including a degradation control region selected to achieve a desired degradation period, the polymer also including a cross-linking group selected to achieve a desired cross-linking period, and

instructions for forming a mixture of the protein solution and polymer solution and for applying the mixture to embolize an arterio-venous malformation.

69. A system according to claim 68

wherein the cross-linking group is selected to achieve a desired cross-linking period of approximately 30 to 120 seconds.

70. A system for forming a biocompatible material comprising

a protein solution,

a polymer solution including a derivative of a hydrophilic polymer with a functionality of at least three, wherein, upon mixing, the protein solution and the polymer solution cross-link to form a non-liquid, three-dimensional network that degrades over time back to a liquid form, the polymer including a degradation control region selected to achieve a desired degradation period, the polymer also including a cross-linking group selected to achieve a desired cross-linking period, and

instructions for forming a mixture of the protein solution and polymer solution and for applying the mixture to fill an aneurysm.

71. A system according to claim 70

wherein the degradation control region is selected to achieve a desired degradation period of approximately one year.

72. A system according to claim 70 or 71

wherein the cross-linking group is selected to achieve a desired cross-linking period of approximately 5 to 30 seconds.

73. A system for forming a biocompatible material comprising

a protein solution,

a polymer solution including a derivative of a hydrophilic polymer with a functionality of at least three, wherein, upon mixing, the protein solution and the polymer solution cross-link to form a non-liquid, three-dimensional network that degrades over time back to a liquid form, the polymer including a degradation control region selected to achieve a desired degradation period, the polymer also including a cross-linking group selected to achieve a desired cross-linking period, and

instructions for forming a mixture of the protein solution and polymer solution and for applying the mixture to deliver a pharmaceutical.

74. A system according to claim 73

wherein the degradation control region is selected to achieve a desired degradation period of approximately one year.

75. A system according to claim 73 or 74

wherein the cross-linking group is selected to achieve a desired cross-linking period of approximately 5 to 30 seconds.

76. A system for forming a biocompatible material comprising

a protein solution,

a polymer solution including a derivative of a hydrophilic polymer with a functionality of at least three, wherein, upon mixing, the protein solution and the polymer solution cross-link to form a non-liquid, three-dimensional network that degrades over time back to a liquid form, the polymer including a degradation control region selected to achieve a desired degradation period, the polymer also including a cross-linking group selected to achieve a desired cross-linking period, and

instructions for forming a mixture of the protein solution and polymer solution and for applying the mixture to deliver cells.

77. A system according to claim 76

wherein the degradation control region is selected to achieve a desired degradation period of approximately 1 week to 6 months.

78. A system according to claim 76 or 77

wherein the cross-linking group is selected to achieve a desired cross-linking period of approximately 5 to 30 seconds.

79. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the degradation control region comprises at least one selectable hydrolytically degradable moiety.

80. A system according to claim 79

wherein the hydrolytically degradable moiety includes saturated di-acids, unsaturated di-acids, poly(glycolic acid), poly(DL-lactic acid), poly(L-lactic acid), poly(ξ-caprolactone), poly(δ-valerolactone), poly (γ-butyrolactone), poly(amino acids), poly(anhydrides), poly(orthoesters), poly(orthocarbonates), or poly (phosphoesters).

81. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the degradation control region comprises at least one selectable enzymatically degradable moiety.

82. A system according to claim 81

wherein the enzymatically degradable moiety includes Leu-Glyc-Pro-Ala (collagenes sensitive linkage) or Gly-Pro-Lys (plasmin sensitive linkage).

83. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the cross-linking group is selected to react with at least one thiol.

84. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the cross-linking group is selected from a group consisting essentially of vinyl sulfone, N-ethyl maleimide, iodoacetamide, and orthopyridyl disulfide.

85. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the cross-linking group is selected to react with at least one amine.

86. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the cross-linking group is selected from a group consisting essentially of aldehydes.

87. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the cross-linking group is selected from a group consisting essentially of active esters, epoxides, oxycarbonylimidazole, nitrophenyl carbonates, tresylate, mesylate, tosylate, and isocyanate.

88. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the cross-linking group includes an ester of N-hydroxysuccinimide.

89. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the protein solution includes a buffer.

90. A system according to claim 89

wherein the buffer includes carbonate or phosphate.

91. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the polymer comprises a compound of the formula PEG-(DCR-CG)$_n$, where PEG is poly(ethylene glycol), DCR is the degradation control region, CG is the cross-linking group, and n is equal to or greater than three.

92. A system according to claim 91

wherein the compound comprises a multi-armed polymer structure.

93. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the protein solution comprises at least one non-immunogenic, hydrophilic protein.

94. A system according to claim 93

wherein the non-immunogenic, hydrophilic protein is selected from a group consisting essentially of serum, serum fractions, and solutions of albumin, gelatin, antibodies, fibrinogen, and serum proteins.

95. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the protein solution comprises at least one

water soluble derivative of a hydrophobic protein.

96. A system according to claim 95

wherein the water soluble derivative of a hydrophobic protein is selected from a group consisting essentially of comprising solutions of collagen, elastin, chitosan, and hyaluronic acid.

97. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the protein solution comprises at least one hybrid protein.

98. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the protein solution comprises at least one synthetic amino acid sequence.

99. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the protein solution comprises recombinant or natural human serum albumin.

100. A system according to claim 99

wherein the human serum albumin is at a concentration of about 25% or less.

101. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the polymer solution includes a derivative of a polymer selected from a group consisting essentially of poly(ethylene glycol), poly(ethylene oxide), poly(vinyl alcohol), poly(vinylpyrrolidone), poly(ethyloxazoline), poly(ethylene glycol)-co-poly(propylene glycol) block copolymers, or electrophilically derivatized polysaccharides, carbohydrates, or proteins.

102. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the polymer solution comprises at least one hybrid protein.

103. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the polymer solution comprises at least one synthetic amino acid sequence.

104. A system according to claim 44 or 47 or 50 or 53 or 56 or 59 or 62 or 65 or 68 or 71 or 73 or 76

wherein the polymer is comprised of poly(ethylene glycol)(PEG).

105. A system according to claim 104

wherein the PEG has a molecular weight of between about 1,000 and about 30,000 g/mole.

106. A system according to claim 104

wherein the PEG has a molecular weight of between about 2,000 and about 15,000 g/mole.

107. A system according to claim 104

wherein the PEG has a molecular weight of between about 10,000 and 15,000 g/mole.

108. A system according to claim 104

wherein the PEG comprises a multi-armed polymer structure.

109. A biocompatible material comprising a mixture of a protein solution and a polymer solution which, upon mixing, cross-link to form a non-liquid, three-dimensional network, and an agent that undergoes color change in response to cross-linking of the mixture.

110. A material according to claim 109

wherein the agent undergoes color change in response to change in pH.

111. A material according to claim 109

wherein the agent exhibits a first color when the mixture is in a liquid state and a second color, different than the first color, when the mixture forms the non-liquid, three-dimensional network.

112. A material according to claim 109

wherein the agent exhibits a first color when the

mixture is in transition between a liquid state and the non-liquid, three dimensional network, and a second color, different than the first color, when the mixture forms the non-liquid, three-dimensional network.

113. A material according to claim 109 wherein the agent includes xylenol blue.

114. A material according to claim 109 wherein the agent includes phenol red.

115. A material according to claim 109 wherein the agent includes a mixture of xylenol blue and phenol red.

116. A material according to claim 109 wherein the agent includes phenolphthalein.

117. A material according to claim 109 wherein the agent includes o-cresolphthalein.

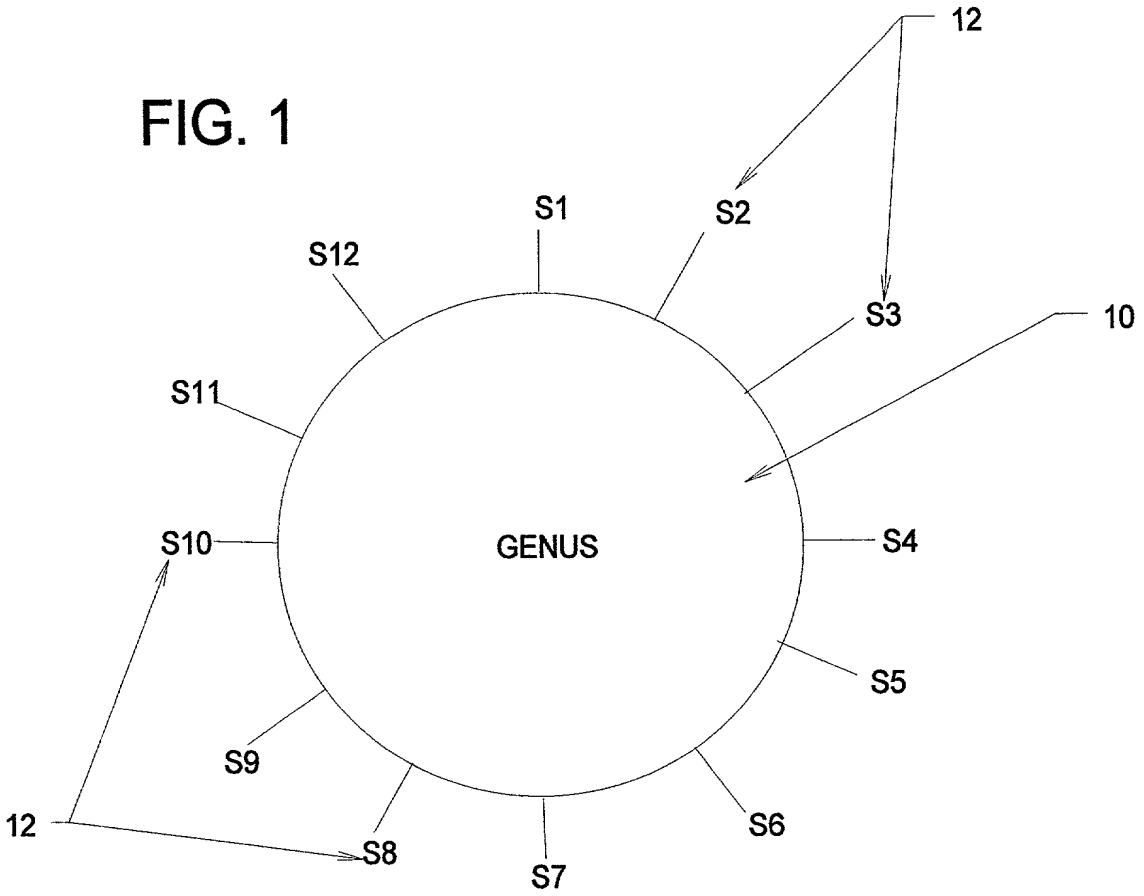
118. A material according to claim 109 wherein the agent includes bromothymol blue.

119. A material according to claim 109 wherein the agent includes a mixture of bromothymol blue and phenolphthalein or o-cresolphthalein.

ABSTRACT

A biocompatible material genus serves as the foundation for multiple material composition species, each adapted to a specific therapeutic indication.

FIG. 1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S1
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GENUS
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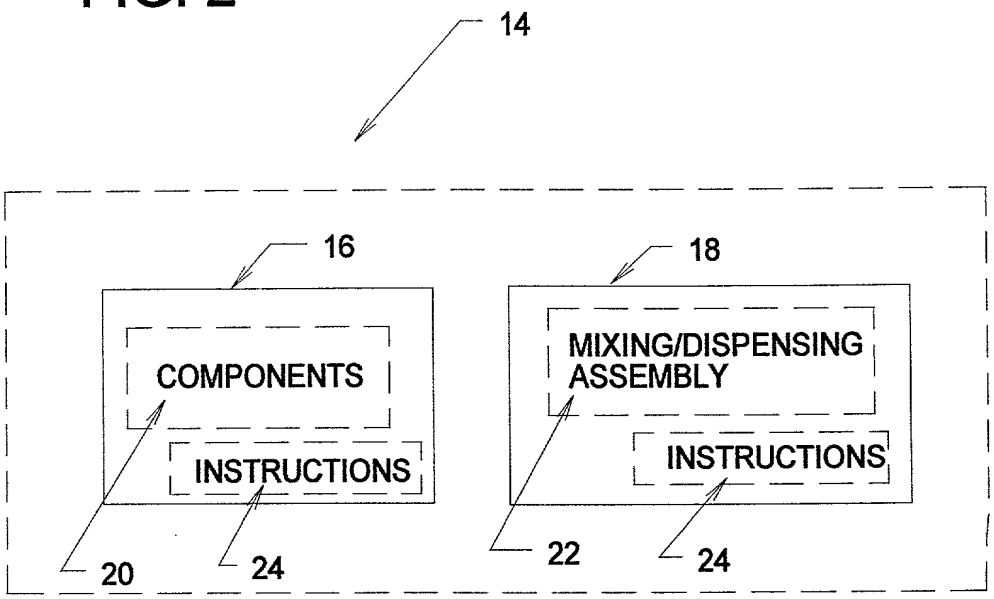
FIG. 2


14
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COMPONENTS
MIXING/DISPENSING ASSEMBLY
INSTRUCTIONS
INSTRUCTIONS
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24
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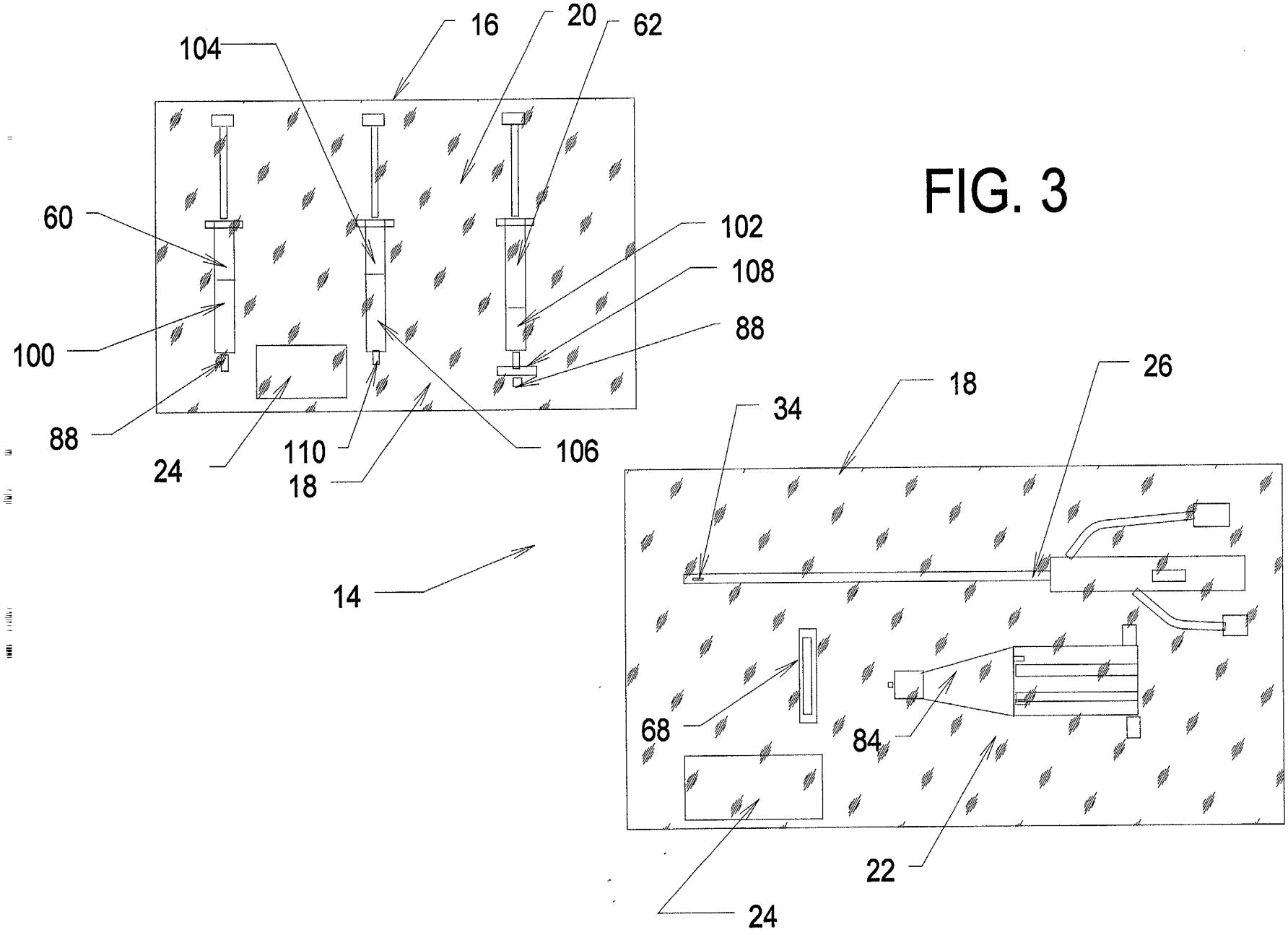
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FIG. 3

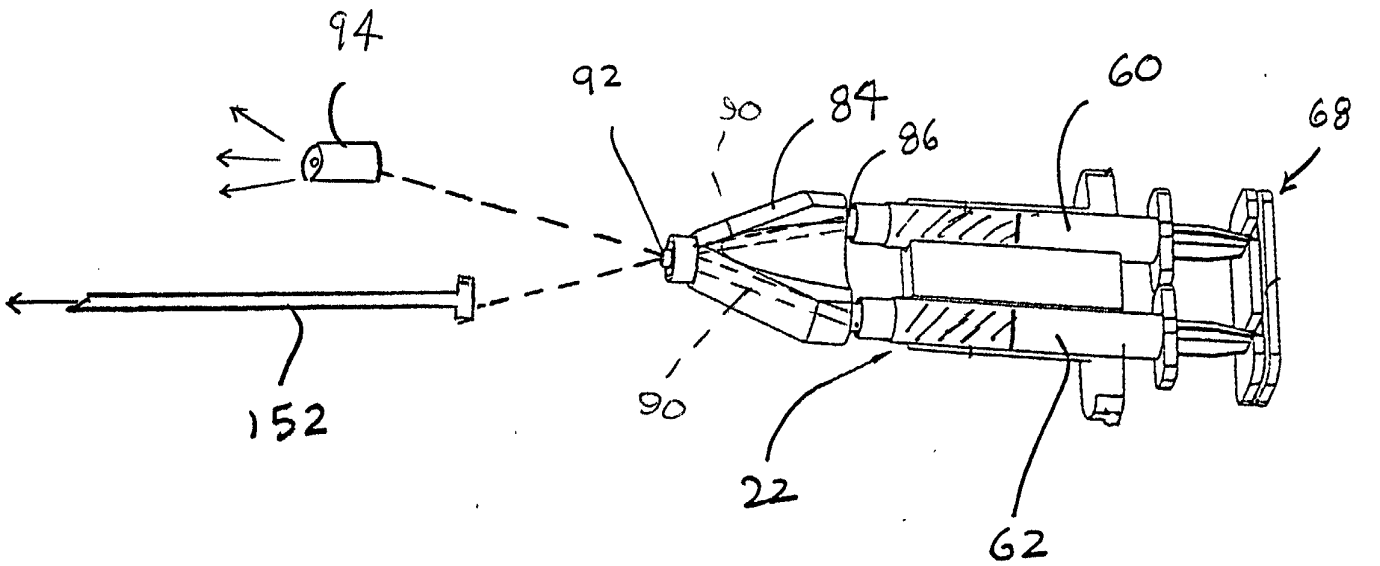

FIG. 4

FIG. 5

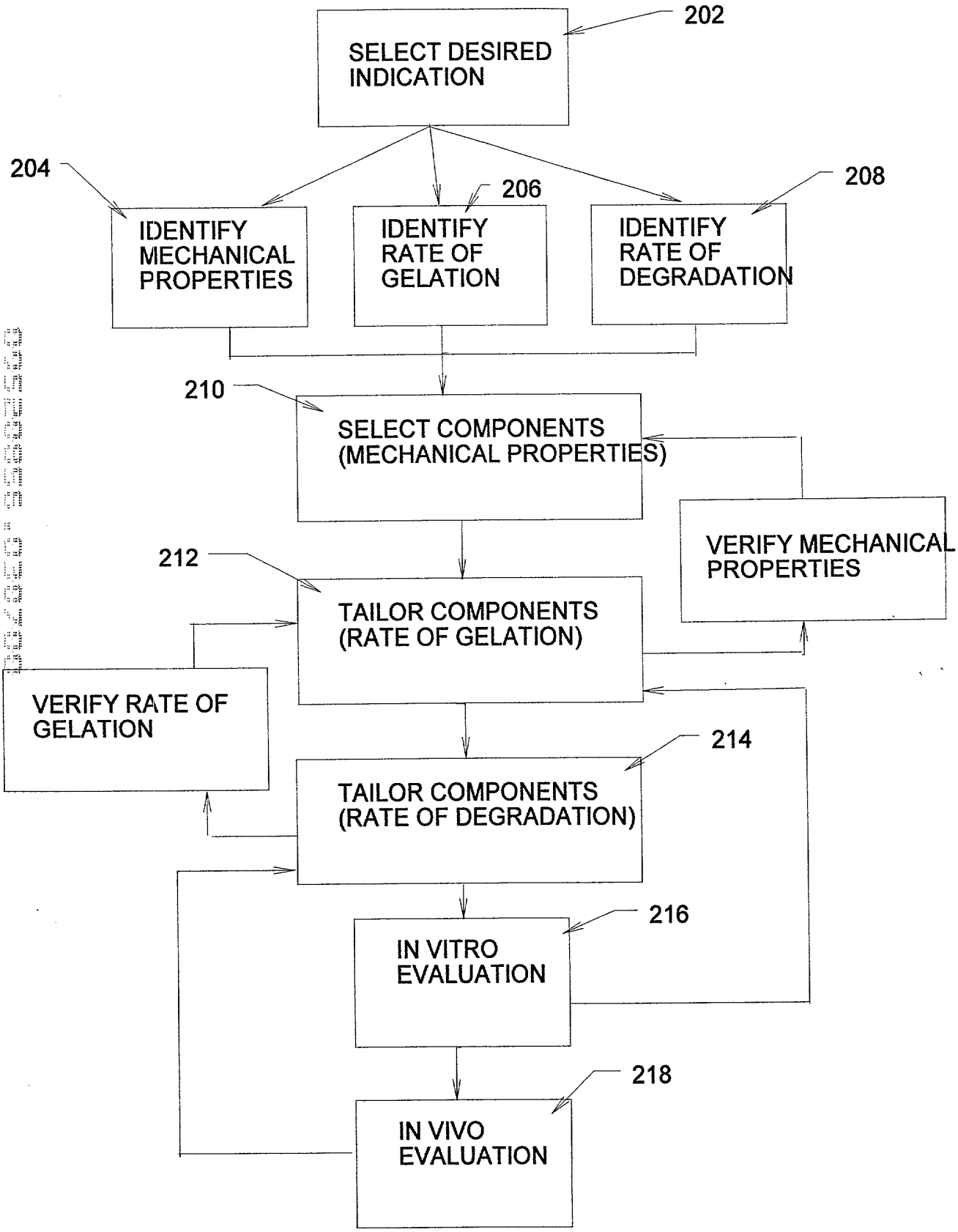
SELECT DESIRED INDICATION
202
204
206
208
IDENTIFY MECHANICAL PROPERTIES
IDENTIFY RATE OF GELATION
IDENTIFY RATE OF DEGRADATION
210
SELECT COMPONENTS (MECHANICAL PROPERTIES)
VERIFY MECHANICAL PROPERTIES
212
TAILOR COMPONENTS (RATE OF GELATION)
VERIFY RATE OF GELATION
214
TAILOR COMPONENTS (RATE OF DEGRADATION)
216
IN VITRO EVALUATION
218
IN VIVO EVALUATION

FIG. 6